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EXPERIMENTAL OBSTRUCTIVE JAUNDICE

ITS EFFECT ON FIBRINOGEN AND COAGULATION OF THE BLOOD

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The scientific explanation of the hemorrhagic tendency in patients suffering with jaundice has been energetically sought for by a great number of investigators, some of whom are apparently definitely convinced by the results of their experimental work that the problem is settled. It is difficult for one reviewing the literature to come to any definite conclusion in his own mind relative to this phenomenon, because of the wide diversity of opinions and because of the conflicting data in the literature.

The fibrinogen content of the blood plasma has not been investigated carefully from an experimental standpoint as a possible cause for this hemorrhage, and it was with that in mind that the work herein submitted was done in an attempt to arrive at some solution of this perplexing and vexing problem.

After considering this subject theoretically, it seems that the hemorrhagic tendency in these patients might be attributed to the presence of abnormal amounts of fibrinogen, which plays such a prominent rôle in the coagulation of the blood. It is conceded that the greater part of the blood fibrinogen has its origin in the liver, and the fibrinogen content of the plasma has been shown to vary with conditions of the liver. It is assumed, of course, that obstruction to the outflow of bile by the normal route causes more or less hepatic damage.

The restoration of fibrinogen to its normal level in the blood after depletion from any cause, e. g., bleeding, is almost exclusively accomplished by the liver, as was indicated by Howe.[1] Mann and Bollman [2] demonstrated that following complete extirpation of the liver the fibrinogen of the blood did not return to its normal level after bleeding. Recent investigations, particularly those of Howe,[3] point to the liver as the main source of supply of fibrinogen.

1. Howe: J. Biol. Chem. **57**:235 (Aug.) 1923.
2. Mann and Bollman: Proc. Staff Meet., Mayo Clin. **4**:328 (Nov.) 1929.
3. Howe: Physiol. Rev. **5**:439, 1925.

Whipple attributed the origin of fibrinogen to the liver. Foster and Whipple[4] found that the fibrinogen content of the plasma is reduced by measures that cause destruction of hepatic tissue. McMaster and Drury[5] further confirmed the fact that fibrinogen is of hepatic origin. The blood of normal animals was defibrinated and reinjected, and it was found that 90 per cent of the normal fibrinogen content was present in six hours. When hepatectomized animals were treated in the same way, there was noted a slight rise of fibrinogen in from four to five hours, presumably from a reserve in the tissues, but after from four to five hours the fibrinogen content decreased until death. It was concluded that without the liver the organism apparently has no power to regenerate fibrinogen.

On the basis of the aforementioned results and similar personal observations, Full,[6] McLester[7] and many others concluded that the fibrinogen content of the plasma may be used as an index to hepatic function. Peters and Van Slyke[8] contended that decrease in fibrinogen content does not parallel the degree of destruction of the liver. They admitted, however, that severe injury to the liver is, in a number of cases, attended with decrease in plasma fibrinogen. Foster and Whipple[4] showed that inflammatory and destructive lesions of the liver cause an increase in fibrinogen as would a normal stimulus. When the loss of liver substance is so great that the organ can no longer meet the demands of the body, fibrinogen decreases.

Wiener and Wiener[9] conceded that changes in the permeability of the endothelium may be responsible for, or may influence, the change in concentration of fibrinogen in the plasma. Peterson assumed that the capillaries govern permeability by highly specialized function. Their endothelial walls act as an "ultrafilter," and any changes in their structure should result in altered concentrations of the various materials that are allowed to pass. Permeability of the capillaries depends on permeability of the endothelial cells in the walls of the vessels. An increase in this permeability may be caused by dilatation from physical, nervous or chemical stimuli (Krogh[10]) and by increased

4. Foster and Whipple: Am. J. Physiol. **58**:407, 1922.

5. McMaster and Drury: Proc. Soc. Exper. Biol. & Med. **26**:490, 1929.

6. Full: Verhandl. d. Kong. f. inn. Med. **33**:201, 1921.

7. McLester: Diagnostic Value of Blood Fibrin Determinations with Special Reference to Disease of the Liver, J. A. M. A. **79**:17 (July 1) 1922.

8. Peters and Van Slyke: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931.

9. Wiener and Wiener: Plasma Proteins, Arch. Int. Med. **46**:236 (Aug.) 1930.

10. Krogh: Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1923, p. 230.

capillary pressure or injury (Landis [11]). The viscosity of fibrinogen is known to be greater than that of the serum proteins, and the permeability of hepatic endothelium is said to be greater than that of any other endothelium. Wiener and Wiener,[9] after an exhaustive study of fibrinogen and serum proteins in man, concluded that the physiologic limits of the concentration of fibrinogen in the plasma are at wide variance. Their reports, from investigation of the amounts of these substances in various physiologic and pathologic conditions, show that the fibrinogen is slightly increased during menstruation and definitely increased during the later months of pregnancy and during the puerperium. They concluded further that any irritation of the liver, i. e., slight infections, exposure to the x-rays, ingestion of chloroform and phosphorus in small doses and all inflammatory processes, produces an increase in the fibrinogen content of the plasma. In cirrhosis of the liver, they found a slight increase early in the process, but a decrease or low ·normal fibrinogen content later, whereas concurrent infections elsewhere in the body caused only slight increases. In the presence of jaundice without pyrexia, the concentration of fibrinogen was found to be within normal limits. In cholecystitis, the findings are similar to those in infections. Pickering [12] also noted a definite decrease in fibrinogen content of the plasma in cases of cirrhosis of the liver. Whipple and Hurwitz [13] showed that small doses of chloroform and phosphorus increase the coagulability of the blood and increase the fibrinogen content of the plasma, but that large doses of these "liver poisons" produce the opposite effect.

There has been a great deal of controversy among investigators in the clinical field, as well as among those in the experimental laboratory, concerning the cause of hemorrhage in jaundiced patients. Most of the work that has been done has been to determine whether or not fluctuation in the calcium content of the serum occurs, and whether or not these changes affect coagulability of the blood in jaundiced patients.

In reviewing the literature it is difficult, because of the vast difference in opinions, for one to obtain any established facts concerning the effect that calcium content of the blood has on coagulability. These opinions are based on results obtained in the clinic and the laboratory : thus it is impossible to conclude that any constant relationship exists. Halverson, Mohler and Bergeim [14] reported a slight reduction in calcium

11. Landis: Am. J. Physiol. **81**:124, 1927.

12. Pickering: The Blood Plasma in Health and Disease. New York, The Macmillan Company, 1928, p. 24.

13. Whipple and Hurwitz: J. Exper. Med. **13**:136, 1911.

14. Halverson, Mohler, and Bergeim: Calcium in the Blood in Tuberculosis, J. A. M. A. **68**:1309 (May 5) 1917.

content of blood serum in jaundice. The reduction noted was considered more apparent than real. Koechig [15] arrived at the same conclusion. Walters and Bowler,[16] Snell, Greene and Rowntree [17] and Zimmerman [18] found no change in serum calcium in obstructive or other types of jaundice. Kirk and King [19] reported moderate reductions in total calcium, but greater reductions in diffusible calcium, emphasizing the importance of the rôle that the diffusible, or ionizable, calcium plays in coagulation. Emerson [20] corroborated the findings of Kirk and King by a series of experiments, and called attention to the fact that the probable source of error obtained by other investigators was the disregard of the effect of ether anesthesia. He demonstrated that specimens of blood taken during or shortly after ether anesthesia show an increase in calcium content of the serum. The experimental results obtained by Emerson are not fraught with this error. He showed that in jaundice the serum calcium is diminished concomitantly with diminished coagulability of the blood, and he was able to restore calcium to the normal level by administration of calcium salts in therapeutic doses. Emerson also found an increase in serum calcium in animals with biliary fistulas. Buchbinder and Kern [21] found no alteration in serum calcium after ligation of the common bile duct of the adult dog, but a progressive decrease after the same procedure in the puppy. Subsequently, these same authors found that, after producing obstructive jaundice in thyroparathyroidectomized animals, there resulted a diminution or an absence of tetany. The period of survival of the animals suffering with tetany was prolonged if the jaundice was maintained over a considerable length of time. If, after removal of the parathyroid glands, the animals were subjected to "acute" jaundice, they suffered with severe and terminal tetany. The conclusion was drawn that tetany was altered by obstructive jaundice, on the basis of (1) the response of the thyroparathyroidectomized animal, (2) the relief from tetany following intravenous injection of bile and (3) the absence of tetany in late obstructive jaundice in the puppy with calcium at the tetanic level. One is here reminded of the action of bile as a depressant of the central

15. Koechig: J. Lab. & Clin. Med. **9**:679 (July) 1924.

16. Walters and Bowler: Surg., Gynec. & Obst. **39**:200 (Aug.) 1924.

17. Snell; Greene, and Rowntree: Diseases of the Liver: Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, Arch. Int. Med. **36**:273 (Aug.) 1925.

18. Zimmerman: Am. J. M. Sc. **174**:379 (Sept.) 1927.

19. Kirk and King: J. Lab. & Clin. Med. **11**:928 (July) 1926.

20. Emerson: J. Lab. & Clin. Med. **14**:122 (Nov.) 1928.

21. Buchbinder and Kern: Experimental Obstructive Jaundice: II. Modification of the Parathyroid Tetany Mechanism in Jaundice, Arch. Int. Med. **41**:754 (May) 1928.

nervous system; i. e., it raises the threshold of nervous excitability. Snell and Greene [22] emphasized the fact that there is no agreement concerning the variation in the calcium content of the serum in jaundice. They found that in jaundice all the fractions of the serum calcium—the total, the nondiffusible and the diffusible—are equally affected. They concluded that the amount of alteration in the diffusible calcium of jaundiced patients is not significant. The coagulation time was not considered by Snell, Greene and Rowntree, but they expressed the belief that it is affected by calcium in some more complicated mechanism rather than directly. The variation in dogs and patients was reported insignificant. Gunther and Greenberg [23] stated that a review of the literature produced no proof of a deficiency of available calcium in the blood of jaundiced patients, nor any direct proof of a deficiency of diffusible calcium in the serum. They observed in jaundiced patients a diminution in the nondiffusible calcium, but parallel with this was a loss of serum albumin accounted for by a decrease in total serum proteins. They contended that this cannot be interpreted as an indication of a deficiency of available calcium. They found that the concentration of nondiffusible calcium was low in a few patients with jaundice, but that there was an accompanying lowered concentration of serum albumin. and that the concentration of neither serum albumin nor nondiffusible calcium fluctuated with the degree of jaundice. The nondiffusible fraction of serum calcium was considered to be low as a result of the low serum albumin. It was shown that the value of diffusible calcium is a more accurate measure of the physiologically available calcium than the value of either the nondiffusible or the total calcium fraction in the serum. Gunther and Greenberg contended that factors other than alteration in the amount of available calcium must be sought for to explain satisfactorily abnormal bleeding in jaundiced patients. Waltman Walters,[24] recently, in an excellent treatise on obstructive jaundice. presented evidence to the effect that calcium, given in therapeutic dosage. is rapidly excreted by the kidneys. It does not accumulate in the blood. and the normal level of the serum calcium is restored in two hours.

Ravdin, Riegel and Morrison [25] compared the relative merits of calcium and dextrose as hemostatic agents in the presence of jaundice. and agreed with Bancroft, Kugelmass and Stanley-Brown [26] that coagu-

22. Snell and Greene: Am. J. Physiol. 92:630 (April) 1930.

23. Gunther and Greenberg: I. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, Arch. Int. Med. 45:983 (June) 1930.

24. Walters, Waltman: Obstructive Jaundice: Physiological and Surgical Aspects, Rochester, Minn., Mayo Foundation, University of Minnesota, 1931.

25. Ravdin; Riegel, and Morrison: Ann. Surg. 91:801 (June) 1930.

26. Bancroft; Kugelmass, and Stanley-Brown: Ann. Surg. 90:161, 1929.

lation and bleeding times are of little value in determining a hemorrhagic tendency. They claimed that, in spite of the agitation favoring the use of calcium in cases of obstructive jaundice, no one has clinically demonstrated a deficiency of serum calcium in these cases. Dextrose is used, and it was suggested that it may help in restoration and repair of the damaged liver. They cited Minot and Cutler's [27] demonstration of the beneficial effect of the use of calcium in dogs with hepatic degeneration, in the blood of which there occurred, as a result of this disease, an increase in guanidine and like substances. They took issue with Partos and Svec [28] in their contention that hyperglycemia results from the use of calcium, on the ground that it does not occur consistently. Nevertheless, they found that calcium therapy was efficacious in diminishing the damage to the liver produced by biliary obstruction. Schreiber [29] and Kehr [30] suggested the use of dextrose preoperatively in cases of jaundice. Since 1920, the use of this substance has become widespread. Walters [31] and Whipple [32] advocated the use of dextrose and calcium and considered dextrose of primary importance as regards the reduction of mortality from surgical operations. Davis, Hall and Whipple [33] asserted that a diet high in carbohydrate would affect regeneration of hepatic tissue at the rate of 100 Gm. daily. Ravdin et al.[25] stated that a diet high in carbohydrate causes more rapid restoration of hepatic structure after release of biliary obstruction and exerts a definitely favorable effect while obstruction exists. They stated that clinical patients whose blood has a prolonged clotting time have severe hepatic damage. Mann, Bollman and Markowitz [34] showed in hepatectomized animals that there occurs: (1) a variable change in coagulation of the blood; (2) a diminution of fibrinogen content, after depletion of the latter from hemorrhage, with partial or no restoration of the same, and (3) no parallelism between fibrinogen content and coagulability of the blood. The latter point was confirmed by work on normal and jaundiced dogs by Ravdin, Riegel and Morrison.[25] Minot and Cutler [27] demonstrated in dogs an increase in guanidine content of the blood associated with hypoglycemia in the presence of jaundice. Ellis [35] showed that

27. Minot and Cutler: Proc. Soc. Exper. Biol. & Med. **26**:607, 1929.

28. Partos and Svec: Arch. f. d. ges. Physiol. **218**:209, 1930.

29. Schreiber: Zentralbl. f. Chir. **2**:1200, 1913.

30. Kehr: Ergebn. d. Chir. u. Orthop. **8**:471, 1914.

31. Walters: Surg., Gynec. & Obst. **33**:651, 1921.

32. Whipple: S. Clin. North America **1**:373, 1921.

33. Davis; Hall, and Whipple: The Rapid Construction of Liver Cell Protein on a Strict Carbohydrate Diet Contrasted with Fasting: Mechanism of Protein-Sparing Action of Carbohydrate, Arch. Int. Med. **23**:689 (June) 1919.

34. Mann; Bollman, and Markowitz: Am. J. Physiol. **90**:445, 1929.

35. Ellis: Biochem. J. **22**:353 and 930, 1928.

dextrose protects the experimental animal from toxemia due to guanidine, definitely proving that it is of value in a restorative rôle. Partos and Svec [28] proved that substances which increase the coagulability of the blood mobilize glycogen and produce hyperglycemia, and that substances prolonging the coagulation time cause hypoglycemia. Cannon and Gray [36] showed that epinephrine causes increase in blood sugar and increase in coagulability of the blood. Rabinovich [37] demonstrated that the coagulation time was diminished following anesthesia, and emphasized the fact that during the first fifteen minutes of anesthesia the blood sugar increases. Boldyreff,[38] followed by Turcatti,[39] expressed opinions opposite to these. Boldyreff stated that with complete loss of pancreatic secretion there is a rise in blood sugar with diminution in coagulability of the blood. Ravdin, Riegel and Morrison [25] stated that hyperglycemia does not increase the coagulability of the blood in all cases, but that hyperglycemia and increase in the coagulability of the blood are present in a great many cases. They suggested that dextrose has the effect of stimulating the formation of fibrinogen, but their experimental data do not bear out this assumption. Svec [40] injected insulin into experimental animals, producing hypoglycemia, which was followed by diminution in coagulability of the blood. Partos [41] confirmed these results, and showed that diabetic animals had increased coagulability of the blood. He was able to produce similar effects by administration of epinephrine hydrochloride to one series of depancreatized dogs and morphine to another series. Walters [24] stated that he considers the preoperative administration of dextrose to be of extreme importance in these cases. He also favors small doses of calcium chloride (5 grains [0.32 Gm.]), intravenously, for three days prior to operation.

Heparin has been investigated in Howell's laboratory. Howell [42] said that diminution of the heparin in the blood is probably the cause of bleeding in hemophilia, jaundice and other such pathologic conditions. This cannot be proved, however, until a method has been devised for quantitative estimation of heparin. Heparin is present in the blood in such small quantities that it is difficult to obtain it even qualitatively. Up to the present time there has been no method submitted for its quantitative determination.

36. Cannon and Gray: Am. J. Physiol. **34**:232, 1914.
37. Rabinovich: Brit. J. Exper. Path. **8**:343, 1927.
38. Boldyreff: Am. J. M. Sc. **177**:778, 1929.
39. Turcatti: Compt. rend Soc. de biol. **100**:116, 1929.
40. Svec: Arch. f. d. ges. Physiol. **224**:62, 1930.
41. Partos: Arch. f. d. ges. Physiol. **224**:448, 1930.
42. Howell: Am. J. Physiol. **77**:689 (Aug.) 1926.

Howell and Holt [43] showed that heparin does not react with calcium salt, but that there is a thermolabile substance in the blood that reacts with the heparin to form antithrombin. This thermolabile substance can be destroyed by raising the temperature of the blood to 70 C., whereas heparin is not destroyed at 100 C. These authors expressed the belief that heparin is present in the blood under normal conditions. They contended that it is an activator for pro-antithrombin, preventing the formation of thrombin in the normal circulation. By this mechanism, the fluidity of the blood is maintained in the undisturbed vascular system. Heparin also prevents the activation of prothrombin to thrombin, according to Howell and Holt.[43] Thus, by means of a double mechanism, this substance is responsible for the prevention of intravascular clotting. Howell [42] expressed the belief that the presence of an abnormal amount of heparin may be responsible for the hemorrhagic tendency of patients with hemophilia and jaundice.

Howell,[44] in a still later publication, again claimed for heparin all the possibilities for which he contended in the previous article. He showed that it was increased in the blood by intravenous injection of peptone. He also found that in shed blood its action was neutralized by the phosphatid material furnished by the corpuscles or tissue cells. Howell found that the antithrombin is increased by intravenous administration of heparin.

Stuber and Lang [45] stated that heparin inhibits coagulation of the blood by inhibition of glycolysis. They observed that, following its injection, there was a decrease in coagulability of the blood, along with a decrease in glycolysis.

The tissue extracts and their place in the coagulation process have been thoroughly investigated by Mills.[46] The first attempts made at isolation of their thromboplastic elements were made by Wooldridge,[47] who found that the thromboplastic action of these extracts is due to a phospholipin, which, he determined, was a lecithin. In Howell's laboratory this was found to be cephalin (Mills). Mills [46] demonstrated that it is present in all organs but to a greater extent in the lung. He contended that, in addition to the phospholipoid material. the presence of the protein component of the tissue extracts is necessary for the manifestation of the maximum potency of the thromboplastic agents. The intravenous injection of phospholipin and the protein component of the tissues produces intravascular clotting and death.

43. Howell and Holt: Am. J. Physiol. **47**:328, 1919.

44. Howell: Am. J. Physiol. **71**:553 (Feb.) 1925; Bull. Johns Hopkins Hosp. **42**:199 (April) 1928.

45. Stuber and Lang: Biochem. Ztschr. **212**:16, 1929.

46. Mills: J. Biol. Chem. **40**:425 (Dec.) 1919.

47. Wooldridge, L. C.: On Chemistry of the Blood and Other Scientific Papers, London, Kegan Paul, Trench, Trübner & Co., 1893.

EXPERIMENTAL WORK

In selecting animals for this experimental work, it was decided that dogs would be most suitable. The biliary system of the dog is quite similar to that of man.

The greatest difficulty confronting one, in producing experimental obstructive jaundice in dogs, is the presence of accessory bile ducts. Occasionally, one or more hepatic ducts empty directly into the duodenum. Rarely, there is a duct from the gallbladder opening into the duodenum. It is necessary to interrupt every channel carrying bile from the liver in order to produce jaundice that will persist. There are so many branches joining the various bile ducts that the duct or ducts, overlooked at one operation, following which the jaundice subsides, are found at the time of the second operation to be enormously dilated. These enlarged channels apparently are sufficient to allow passage of the noxious bile to the duodenum. In the course of two or three days the stagnation is relieved and the jaundice disappears.

Dogs suffering with obstructive jaundice succumb within a relatively short period of time. Therefore, few of the observations are made in the presence of long-standing cholemia.

Twenty-seven animals were subjected to acute obstructive jaundice. The common bile duct and accessory ducts, when present, were divided between ligatures. On the third or fourth day each dog suffered with jaundice that could be recognized clinically. There was an icteric discoloration of the conjunctivae and skin. The feces became putty-colored or clay-colored and typically acholic, and biliuria was present. The dogs were perceptibly ill, and severe toxemia was evident.

Six of the dogs died before biliary obstruction had begun to produce a marked effect. One dog died on the operating table, as the result of pulmonary collapse. There was a diaphragmatic hernia on the right side, with the spleen, omentum and one lobe of the liver in the right pleural cavity. As this hernia was reduced, collapse of both lungs occurred. A rent was found in the mediastinal pleura, probably secondary to collapse of the right lung. Collapse of the left lung followed. Another animal died the day following operation. The cause of death was given as asthenia. Probably operative trauma played its part here, too, as the duct was located and ligated with considerable technical difficulty. Three dogs suffered evisceration and succumbed as the result of self-mutilation, followed by hemorrhage One died three days after operation, the cause of death undetermined. One dog with jaundice died on the eighth day; the cause of death was pneumonia.

Fifteen of the twenty-one animals that lived to show the effects of biliary obstruction died early, the average length of life being 15.7 days. Of the number (twenty-one) that survived to develop jaundice.

twenty-one (100 per cent) died of diffuse hepatitis, the average length of life being 31.6 days. The livers in gross, both on the surface and on section, showed areas of destruction, which were bile-stained. The peritoneum and all viscera were bile-stained.

Determinations of the fibrinogen in the blood plasma were made at intervals during the disease. The Wu method [48] was used. This method may be used with impunity, if one attempts to determine fibrinogen for comparative analysis, as was done in approaching this problem. The figure given by Wu for the tyrosine equivalent for the human being was 16.4. This was calculated on an average of only two determinations, 16 and 16.8, as given in the original publication. It may be realized that, even with the difference of 0.8 in these figures, there exists a considerable variation, and that the percentage of error is not to be overlooked. The tyrosine equivalent for dogs (17.1) was derived from an average of twenty-four normal determinations. There was considerable variation in the different figures that were determined, and an average of these was used. The percentage variation in the end-results was not greater than the percentage variation of the figures for the tyrosine equivalent. Thus the figure, as stated, should hold as a fair multiplicand in the calculation of the fibrinogen values for use on a comparative basis.[49]

In determining the tyrosine equivalent for the dog, twenty-four determinations were made. The values varied from 12.5 to 19.7, and the range of error is rather wide for one to consider using the method without reservation for exact determinations of the fibrinogen content of plasma. It may be added that, in making the last twelve determinations, great care was exercised, and on the filtrate from each specimen two determinations of both nitrogen and tyrosine were made as a check; it was found that the greatest variation in these figures was negligible when the final equivalent figure was calculated.

A table of the averages of the percentage increases in fibrinogen content of the plasma on successive days, with the number of animals on which determinations of this plasma component were made, is appended (table 1). The figure given represents the percentage increase above the normal for each dog.

An average was made of the fibrinogen determinations of each week. The percentage increase (above the average of the normal fibrinogen content for the twenty-seven dogs) for each week was calculated (table 2).

It is evident from the analysis of table 2 that there is a constant increase in the fibrinogen content of the plasma from week to week in

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48. Wu: J. Biol. Chem. **51**:33 (March) 1922.

49. Bliss, Sidney W.: Personal communication.

experimental obstructive jaundice. One must keep in mind, however, that relatively few determinations were made during the fourth week, for reasons that have been given.

The LaMotte-Pigford colorimetric method was used for determination of the icterus index.

The average of the determinations of the icterus index on the dogs before operation was 1.9 units. There was a gradual increase in the

TABLE 1.—*Average Percentage Increase of Fibrinogen in Plasma in Experimental Obstructive Jaundice*

Day	Percentage Increase	Number of Animals
3d	33	2
4th	16	8
5th	63	13
6th	60	4
7th	11	4
8th	27	10
9th	37	2
10th	66	3
11th	50	6
12th	69	1
13th	13	2
17th	12	1
18th	62	6
19th	38	1
20th	57	2
22d	72	1
24th	78	1
25th	58	1
29th	16	2
31st	74	2
32d	12	1
33d	52	1

TABLE 2.—*Average Weekly Percentage Increase of Fibrinogen in Plasma in Experimental Obstructive Jaundice*

Week	Percentage Increase	Number of Animals
1st	44	29
2d	46	29
3d	53	16
4th	62	4

average up to the eighth day. After the eighth day, there began a fluctuation that was not regular. The icterus index varied from 3 to 75 units after the initial increase. During the first, second, third, fourth and fifth weeks, the averages of the icterus indexes were 27, 28, 21, 17 and 35 units, respectively. Whereas the average for the first week was rather low, the highest figures of this determination were consistently noticed in the last two or three days of that week. The average for the fifth day was 26 units; for the sixth day, 32 units; for the seventh day, 52 units. There was a general decrease in the icterus

in the second week, but it was apparently more constant at this time, only varying from 20 to 36 units. During the third week, the icterus index approximated 20 units; during the fourth week, the average was 17 units, and during the fifth week, 35 units.

The coagulation time was estimated by means of the Brodie-Russell-Boggs coagulometer.

It was found that the average normal coagulation time of the twenty-seven dogs was 1 minute and 32 seconds. The coagulation time was

Fig. 1.—This and the graphs in figures 2, 3, 4 and 5 show the variations in fibrinogen content of the blood plasma, coagulation time and icterus index in experimental obstructive jaundice. The solid line represents the fibrinogen content of the plasma in milligrams; the dotted line, the coagulation time in minutes and seconds, and the broken line, the icterus index in units. In this graph are represented the daily averages of these determinations on all of the animals.

found to be consistently increased throughout the experiment, but not in a regular manner. However, the averages for the first, second, third, fourth and fifth weeks were 2 minutes and 35 seconds, 2 minutes and 10 seconds, 1 minute and 54 seconds and 2 minutes and 25 seconds, respectively.

Fig. 2.—Weekly averages of the determinations of fibrinogen, coagulation time and icterus index of all the animals.

Fig. 3.—Record of variations in the determinations for typical animal 1.

Fig. 4.—Record of variations in the determinations for typical animal 2.

Fig. 5.—Record of variations in the determinations for the animal that survived the operation for the longest period.

Fig. 6.—Damaged liver in experimental obstructive jaundice (under high power magnification), showing (a) hyalin-like material, (b) beginning cirrhosis and (c) hepatic necrosis at the periphery. The hepatic parenchyma in this slide was seen to be decidedly damaged.

Fig. 7.—Damaged liver (low power) showing (a) fibrous connective tissue, (b) areas of hepatic cells undergoing degeneration and (c) cells of parenchyma unchanged. These areas, representing the third stage, are much larger than those in either of the two previous stages. The fibrous connective tissue has replaced the hyaline material, except for a few small areas.

As has been stated, the primary cause of death of most of the animals could be attributed only to hepatic degeneration. The livers presented areas of destruction, which were apparent on the surface and on gross section, and which were bile-stained. These areas varied in diameter from 1 mm. to 3 or 4 cm.

The microscopic sections of the livers of the animals that had suffered from the mildest degree of jaundice showed a definitely disarranged hepatic parenchyma in the lobules, but a very small degree of destruction of the cells per se.

Fig. 8.—Damaged liver (high power) showing (*a*) fibroblasts and (*b*) hyaline material. There is seen complete replacement of hepatic parenchyma, and only a few areas of hyaline material remain.

A further lesion, which may be divided into three stages, was observed. These consisted of: 1. Small areas of necrosis, which were infiltrated by leukocytes, the lymphocyte being the predominating cell; polymorphonuclear leukocytes were only occasionally observed. These areas studded the parenchyma throughout, and because of the types of cells found were classified as subacute inflammatory processes. 2. Larger areas than these, including the same cellular elements but, in addition, a hyalin-like material, which predominated (fig. 6). 3. Areas, even larger than those classified under 2, in which cirrhosis was observed, a proliferation of fibrous connective tissue (figs. 7 and 8).

Fig. 9.—Damaged liver (low power) showing (a) central vein of lobule, (b) hepatic necrosis, (c) areas of fatty degeneration and (d) normal hepatic cells at periphery of lobule. In this photomicrograph are represented areas of central necrosis in the lobule. The cells at the periphery are unaffected. This shows the changes that took place in the livers of most of the animals.

Fig. 10.—Areas of fatty degeneration (a) under high power magnification.

Central necrosis of the lobules was present in the greatest number of the animals. This lesion consisted of fatty degeneration (figs. 9 and 10). It was more pronounced in the central part of the lobule for two reasons: first, because the cells in the center of the lobule were the more constantly bathed by the bile, and second, because their blood supply was directly affected owing to injury to the hepatic vessels. The cells at the periphery were unchanged owing to the unimpaired blood supply, the result of an intact portal system and because the bile could be transported more readily from this area for the same reason.

<div align="center">COMMENT</div>

It is evident from the results obtained that no parallelism exists between the fibrinogen content of the blood and the degree of icterus. However, the fibrinogen content of the plasma was high in the first week following obstruction of the extrahepatic bile ducts. The icterus index and coagulation time were also increased during the first week. The fibrinogen content continued to increase during the second and third weeks, whereas the icterus index and coagulation time either decreased or remained stationary. The results obtained during the fourth and fifth weeks are not dependable, because of the fact that comparatively few determinations were made during this stage of the condition.

The increase in the fibrinogen content and the coagulation time during the first week might be considered as the result of the operation, but it is evident that the greatest percentage increase above normal occurred on the fifth day. It seems reasonable that after the first day or so the effect of the operation can be dismissed as a factor in causing this increase. Hueck[50] observed that the fibrinogen content of the plasma was increased after operation.

The results of this experiment have shown that bile is an irritant to the liver and in obstructive jaundice is a stimulus to the formation of more fibrinogen by the liver as is acute inflammation, thus corroborating the results of Wiener and Wiener. It is agreed that this is probably also due to the increase in the permeability of the hepatic endothelium.

It is found that the fibrinogen content of the blood increased considerably just before death, which might be attributed to concentration of the plasma by dehydration.

The fluctuation of the coagulation time is found to coincide with that of the degree of icterus. This was observed in a great majority of the individual animals (figs. 1 and 2). The increase in the icterus indexes is self-explanatory. Following the obstruction in the

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50. Hueck: Arch. f. klin. Chir. **136**:627 (Aug.) 1925.

biliary system the normal exit for the bile was blocked. One is justified in assuming that the reason the icterus decreased after the first week was that a diminution in the amount of bile produced by the liver had occurred, owing to destruction of liver cells.

SUMMARY AND CONCLUSIONS

An attempt has been made to determine whether or not some relationship exists between the fibrinogen content of the plasma, the degree of icterus and the coagulation time of the blood in obstructive jaundice. If some definite relationship exists among these factors, it is reasonable to suppose that it would be enlightening as to the cause of hemorrhage in the presence of jaundice.

It must be stated that as yet there is no adequate proof that any one factor is responsible for this hemorrhage.

Deficiency of calcium in the serum should not be considered as a causative factor in the production of hemorrhage in obstructive jaundice. The results of investigations reported in the literature indicate that a deficiency of calcium is not constant in jaundice, nor is it directly implicated in prolonging the coagulation time.

The contention favoring heparin as a cause for this bleeding is not substantiated by clinical or experimental proof. Little is known of the presence of heparin in the blood, and one can only theorize as to what factors influence the fluctuation of the quantity of heparin present in the circulating blood. The present investigation demonstrates that bile causes destruction of hepatic parenchyma, and the possibility that heparin is increased in the blood in obstructive jaundice is admitted.

It is concluded from this experimental work that the fibrinogen content of the plasma is not decreased in experimental obstructive jaundice. Therefore, hemorrhage in the presence of jaundice is not due to a deficiency of this component of the plasma.

The fibrinogen content of the plasma is increased in acute obstructive jaundice, probably owing to the irritative effect of the bile on the liver.

The coagulation time remained above normal limits in practically all of the determinations, but it did not parallel the fibrinogen content of the plasma. Corroborating the opinion of Ravdin, Riegel and Morrison [25] and Bancroft, Kugelmass and Stanley-Brown.[26] it is concluded that the coagulation time is not a satisfactory index of a hemorrhagic tendency in the presence of jaundice.

The contention of Peters and Van Slyke [8] that a decrease in fibrinogen content of the plasma does not parallel the degree of destruction of the liver is corroborated. It was found that generally an increase in fibrinogen content parallels the extent of damage to the liver.

ROENTGENOLOGY OF EXPERIMENTAL MESENTERIC VASCULAR OCCLUSION

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Mesenteric vascular occlusion still remains one of the most difficult surgical problems. The difficulty in arriving at an early diagnosis undoubtedly accounts for the high mortality, quoted by various writers as being about 70 per cent. The delay in diagnosis is often unavoidable owing to a lack of definite symptoms, even though the damage to the intestinal tract is severe. The same difficulty is experienced in the early clinical diagnosis of simple intestinal obstruction. The effects on the physiology of the bowel of early mesenteric thrombosis or embolism may be compared in some respects with those of simple intestinal obstruction, as well as those of the strangulation type. These conditions result in stasis of the intestinal contents, decrease in the absorption of gas and fluid by the intestinal wall, excretion of fluid into the lumen of the bowel proximal to the affected segment and intestinal hemorrhage and infarction of the involved segment. Although it is an established fact that the roentgen findings of gas and fluid levels in the small intestine have greatly enhanced the diagnosis of simple intestinal obstruction,[1] attention has not been directed to the fact that a similar roentgen picture is produced in mesenteric vascular occlusion.

The object of this paper is to report roentgen studies of experimental occlusion of the mesenteric vessels. The lesions produced in the experimental animals were made to resemble as closely as possible those found in patients.

PATHOLOGY

In the thirty-six cases reported by Larson,[2] 39 per cent of the vascular occlusions were found to be arterial at autopsy, 44 per cent venous and 17 per cent a combination of the two.

1. Swenson, P. C., and Hibbard, J. S.: Roentgenographic Manifestations of Intestinal Obstruction, Arch. Surg. **25**:578 (Sept.) 1932.

2. Larson, L. M.: Mesenteric Vascular Occlusion, Surg., Gynec. & Obst. **53**: 54 (July) 1931.

Klein [3] said that the two types of occlusion are about equally divided. He expressed the belief that arterial occlusion may be caused by either thrombosis or embolism. The etiology of the arterial emboli, which, he stated, include about 2 per cent of cases, must arise in the left side of the heart either from vegetations on the valves or from thrombi in the auricles, as was found in five cases in Larson's series. The arterial thromboses are generally associated with arteriosclerosis, although at times they may be due to pressure of an aortic aneurysm on the artery or to extension of a clot from an aneurysm into the mouth of the artery.

Klein further stated that occlusion of the vein is practically always caused by thrombosis, although some cases are reported in which the etiology is unknown, and others in which only a remote focus of infection exists as a possible cause. The most common cause of venous occlusion is a thrombophlebitis resulting from either acute appendicitis or a pelvic inflammatory condition.

The first effect on the involved segment of intestine of a sudden closure of the superior mesenteric artery, according to most observers, is violent tetanic contractions associated with marked anemia. This condition lasts from two to three hours and is followed by a relaxation and congestion and finally by hemorrhagic infarction. The observations to be reported do not exactly agree with this view. The sequence of events in our experiments was different.

The preliminary contractions were noticed, but numerous subserous hemorrhages varying from 0.25 to 1.5 cm. in diameter resulted within fifteen minutes, and a generalized mild congestion, dilatation and an absence of peristalsis occurred within thirty minutes. This condition was not changed to a great extent at the time the animals were killed, four and six hours later. These phenomena apparently account for the early presence of gas and fluid levels seen in the involved segments on the roentgen film.

Klein stated that all experimenters agree that ligation of the superior mesenteric vein leads constantly to hemorrhagic infarction. He pointed out that in patients the result may be different because it is known that thrombophlebitis generally causes a gradual occlusion. Nevertheless, numerous cases are reported by Larson and others in which an infarcted, congested and soggy segment with dilatation of the proximal intestine was found at operation. These cases would indicate that, although more time is consumed in the process of occlusion, the ultimate outcome is similar to the experimental venous ligations. In the animals of this series, in which the veins to a segment of intestine were ligated, a marked

3. Klein, S.: Embolism and Thrombosis of Mesenteric Artery, Surg., Gynec. & Obst. **33**:385 (Oct.) 1921.

engorgement and a mild contraction immediately occurred, but no relaxation or dilatation followed during the time the abdomen was open. Further, no gas shadows or fluid levels were observed in the involved segment on the roentgen film up to the time the animals were killed, six hours later.

Ligation of both the arteries and the veins of a segment of gut produced the same objective signs that were noted following arterial occlusion, except for the fact that a more marked and rapid congestion and discoloration occurred.

Experimental studies and clinical observations indicate that mesenteric arterial or venous occlusion, severe enough to cause infarction in a segment of intestine, will later cause dilatation of the proximal intestine and result in abdominal distention. These dilated loops of bowel with their fluid levels distributed diffusely over the abdomen will show on the roentgen film.

<div align="center">EXPERIMENTAL DATA</div>

Three groups of dogs were studied in this series of experiments (table). All of the animals were operated on under ether narcosis and with strictly sterile technic. As soon as gas shadows and fluid levels could be demonstrated on the roentgen films, the abdomen was again opened under ether anesthesia, and the condition of the intestine was observed.

In group A, dog 1, the superior mesenteric artery was ligated just distal to the origin of the inferior pancreaticoduodenal artery. In dog 2, the trunk of the superior mesenteric artery was approached through a retroperitoneal route and ligated about 5 cm. distal to its junction with the aorta. Roentgen films of these two animals disclosed gas shadows, and fluid levels were found on the roentgen film early and simultaneously, i. e., at one and one-half and four hours, respectively. At postmortem examination there were numerous areas of discoloration and a mild dilatation.

Four procedures were done in group B. In dog 1, the portal vein was ligated 6 cm. from its entrance into the liver. In dog 2, the tributaries of the superior mesenteric vein from the jejunum, ileum and cecum were ligated. In dog 3, one half of the jejunum and all of the ileum, and in dog 4, about 12 cm. of the lower ileum were included in the occlusion.

In dogs 1, 2 and 3 of this group no roentgen findings were elicited. When the abdomens were opened six and eight hours later, the entire small intestine and its mesentery were found to be mildly edematous and bluish purple, and the lumen of the intestine was filled with blood. The intestine was not dilated. The negative roentgen findings were probably caused by the fact that the extensive hemorrhage into the lumen of the

bowel displaced the gas. Dog 4 showed no effects from the ligation, since the collateral circulation through the longitudinal branches of the anastomosis apparently was adequate. The animal recovered.

Since the negative results in the first two dogs of the foregoing group were probably due to the filling of the intestinal lumen by blood, two more animals were studied in group B. Our object was to produce a definite

Results of Experiments

Experimental Animal	Presence of Gas	Presence of Fluid Levels	Vessels Occluded	Condition of Involved Segment
Group A				
1	4 hours	4 hours	Superior mesenteric artery to ileum and jejunum	Slightly dilated; many subserous hemorrhages; gross color: slightly darkened
2	1½ hours	1½ hours	Superior mesenteric artery to ileum and jejunum	Moderately dilated; many subserous hemorrhages; gross color: slightly darkened
Group B				
1	3½ hours disappeared at 5½ hours	None	Portal vein	Engorged and soggy; bluish red
2	1 hour disappeared at 5 hours	None	Superior mesenteric vein involving jejunum, ileum and proximal colon	Engorged and soggy; bluish red
3	None	None	Superior mesenteric vein involving half of jejunum and ileum	Engorged and soggy; contracted; appendix contained gas and fluid; bluish black
4	None	None	Superior mesenteric vein involving half of ileum	Animal recovered
5	3 hours	5 hours	Superior mesenteric vein involving 10 cm. of ileum	Severe hemorrhage; engorged, edematous and contracted in areas
6	3 hours	5 hours	Superior mesenteric vein involving 10 cm. of ileum	Severe hemorrhage; engorged, edematous and contracted in areas; proximal bowel dilated and contained gas and fluid
Group C				
1	2 hours	6 hours	Superior mesenteric artery and vein to 40 cm. of ileum	4 cm. of ileum engorged and soggy; bluish black; proximal gut slightly dilated
2	2 hours	5 hours	Superior mesenteric artery and vein to 12 cm. of ileum	4 cm. of ileum engorged and soggy; bluish black; proximal gut slightly dilated
3	2 hours	4 hours	Superior mesenteric artery and vein to 12 cm. of ileum	4 cm. of ileum engorged and soggy; bluish black; proximal gut slightly dilated; at 20 hours perforation had occurred; all other cases autopsies at 6 hours

venous occlusion in a relatively short segment of bowel in the lower
ileum. This was accomplished by ligating the mesenteric veins from
10 or 12 cm. of lower ileum and by placing a suture through the mesen-
teric border of the intestine down through the submucosa, thus obliter-
ating the longitudinal anastomosing branches. This procedure was quite
successful in producing a venous occlusion in a small segment of gut.
At postmortem examination, the involved segment and its mesentery

Fig. 1.—Film of the abdomen of a dog in the erect position, in which the
superior mesenteric artery has been blocked as described in the text. Note the
gas shadows and fluid levels, which appeared simultaneously at four hours.

were found to be markedly edematous, hemorrhagic and slightly con-
tracted, and the lumen of the segment and the distal bowel were filled
with blood. The proximal intestine was moderately dilated, and gas
shadows and fluid levels were found on the roentgen film in three hours
and five hours, respectively (fig. 2).

In group C, both the veins and the arteries were occluded in three
animals. In dog 1, the mesenteric arteries and veins were ligated to a

Fig. 2.—Films of the abdomen of a dog in which the tributaries of the superior mesenteric vein, including 12 cm. of the ileum, have been occluded. Note the gas shadows and fluid levels at two and five hours.

Fig. 3.—Films of the abdomen of a dog in which the superior mesenteric arterial branches and venous tributaries have been occluded through 12 cm. of the ileum. Note the gas shadows at two hours and the fluid levels at four and a half hours.

segment of lower ileum about 40 cm. in length, and in dogs 2 and 3, the occlusions involved about 12 cm. of the lower ileum. The roentgen films disclosed gas shadows in two hours and fluid levels in from four to six hours in all animals (fig. 3).

COMMENT

This experimental study indicates that it is possible very early to elicit roentgen signs of intestinal obstruction following mesenteric vascular occlusion.

These signs are indistinguishable from those found in mechanical obstruction. Thus, the differential diagnosis from simple mechanical obstruction cannot be made, of course, on the roentgen findings alone, but involves a careful consideration of the accompanying clinical evidence, particularly as to the existence of possible causes of either condition. On the other hand, the important fact remains that the roentgen evidence of intestinal obstruction appears before abdominal distention can be detected and before damage to the involved segment has become too severe. Except in the cases of extensive venous block in which the damage perhaps is too great in any event for surgical relief, the roentgen examination may be a definite aid in reaching a decision to operate.

SUMMARY

Roentgen examination after experimental occlusion of the mesenteric arteries and veins disclosed gas and fluid levels in dilated loops of small intestine in from two to six hours, which are indistinguishable from those following mechanical intestinal obstruction. However, this evidence should be of aid in early diagnosis and in making an early decision to intervene surgically.

ESTABLISHMENT OF CIRCULATION IN TUBED SKIN FLAPS

AN EXPERIMENTAL STUDY

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The assurance of the circulation of pedunculated skin flaps [1] is of vast importance in plastic surgery. Often it is possible to form a single pedicled flap and to shift it into its new bed immediately. When this is done one must remember that roughly the length of the flap should not be more than two and a half times the width of the pedicle, unless the flap contains an artery, such as the anterior temporal, in which case it may be as long as the artery will nourish and the pedicle may be very narrow, consisting in fact, if necessary, of only the artery and accompanying veins. Frequently much longer flaps are needed than those that can be conveniently made two and a half times the length of the pedicle, and these must often be obtained from an area in which no definite artery is available.

Flaps that are much more than two and a half times as long as the width of the pedicle may be developed by the delayed transfer method. By delayed transfer we mean that in order to assure its circulation a period of time is allowed to elapse between the raising of the flap and its transference to its its new bed. The best type of flap for the delayed transfer is the doubled pedicled flap, and a very satisfactory double pedicled type is that known as the tubed flap, which was developed during the world war by Gillies of London.

The main advantage of the tubed flap, besides its flexibility, is that it is a doubled pedicled flap the circulation of which is assured by the delay in transfer.

1. A skin flap is made up of the whole thickness of the skin with as much of the subcutaneous tissue as is required. It is usually attached at some portion of its periphery by a pedicle, or pedicles, through which it receives its primary blood supply. A skin graft, on the other hand, is a free transplant whose blood supply is entirely derived from the tissue on which it is transplanted.

The question often arises as to the safest time to sever the pedicles of delayed transfer flaps. In other words, when will the circulation of such flaps be sufficiently developed to allow the division of the first pedicle, so that the circulation from the other will be adequate to nourish the flap without loss of tissue.

It is advised by different authors that from several weeks to as many months should be allowed to elapse before dividing one pedicle and making the transfer, but we have felt that in the majority of instances this long delay, while never disadvantageous as far as circulation is concerned, is actually unnecessary. We have allowed some of these flaps to stay as formed for as long as a year and half before dividing one pedicle and then transferring to its new bed. For the purpose of finding out how soon the circulation of a tubed flap adjusted itself and consequently how soon it was safe to divide the pedicle and transfer the flap, we undertook the following series of experiments in the hope that sufficient information might be obtained to be clinically useful.

EXPERIMENTAL STUDY

The development of an adequate blood supply in tubed skin flaps is of paramount importance in the utilization of this type of flap. Before the flap can be implanted in a new location, its blood supply from a single pedicle must be sufficient to nourish the entire flap. This necessitates not only an increase in the size or number of the blood vessels, but also a rearrangement of the vessels, corresponding to the long axis of the flap. The present study was undertaken in an attempt to follow, in chronological order, these changes occurring in the vascular bed.

Investigators, in the past, have concerned themselves chiefly with the development of the blood supply of free skin grafts. The development of the blood supply of whole thickness skin grafts has been worked out and the literature reviewed by Davis and Traut.[2] The effect of variations of orientation of skin grafts, in relation to the axis of their original blood supply has been studied by Paterno.[3] Square full thickness grafts were cut and replaced in their original bed. The control grafts were replaced without changing the orientation of their margins and showed 100 per cent survival with reestablishment of circulation after the second day. Grafts rotated 180 degrees with respect to their original orientation survived completely in 80 per cent and partially in 20 per cent of the cases, with reestablishment of circulation

2. Davis, J. S., and Traut, H. F.: Origin and Development of Blood Supply of Whole Thickness Skin Grafts, Ann. Surg. **82**:871, 1925.

3. Paterno, A.: Influenza della variazione di orientamento del lembo sullo attecchimento e sul ripristino dell circulo sanguino nei trapianti libri autoplastici di cute interna, Ann. ital. di chir. **4**:923, 1925.

retarded until after the fourth day. Grafts rotated 90 degrees from their original position survived completely in 66 per cent of the cases, partially in 20 per cent and failed to survive in 14 per cent. Their circulation was retarded until after the fourth day. These results suggest that the establishment of circulation in skin grafts is partially dependent on the orientation of the vessels of the graft in relation to those of the surrounding structures.

METHODS

In the attempt to study the establishment of a new circulation in tubed flaps, three methods were followed. The first was the determination of the size, number and arrangement of the blood vessels in cleared specimens, removed at intervals of from one to fourteen days following the construction of the tubed flaps. The second method was similar to the first except that an opaque material was injected into the flaps and the studies carried out on roentgenograms of the flaps. The third was a histologic study of the flaps of various ages.

Dogs were used throughout the experiments. The skin of the abdomen was shaved and prepared with iodine and alcohol. With the dogs under ether anesthesia, two double pedicled tubed flaps were outlined, one on either side of the abdominal wall with the long axis of the flap parallel to the long axis of the abdomen. The flaps were 8 to 10 cm. in length and 3 to 3.5 cm. in width, with their bases slightly flared, and were undercut in a manner to include a thin layer of subcutaneous tissue. The edges of the flaps were approximated with interrupted silk sutures, transforming the flaps into tubes with the epithelial surface outside, attached to the abdominal wall at each end in the form of a "valise handle." The skin defect beneath the tubed flap was closed by approximating the opposing skin edges with interrupted silk sutures. Sterile dressings were applied and kept in place for seven days. Usually, healing took place by first intention.

In the first series of experiments, the tubed flaps were separated from the abdominal wall at one end and the animal was given an intravenous injection of from 5 to 10 cc. of 1 per cent solution of toluidine blue, this quantity being sufficient to impart a definite blue color to the skin and mucous membranes. When the blue dye was seen coming from the cut end of the flap, the remaining attachment of the flap to the abdominal wall was cut and the specimen was fixed and cleared, the method [4] of Spalteholz [5] being used. The cleared flaps were then opened along the suture line, spread out flat and mounted in methyl salicylate.

In the second series, the animals were killed, the tubed flaps were separated from the abdominal wall at one end and the injection was made though the aorta. A suspension of barium in gelatin was used as the injection medium.[6] The injection was continued until the barium mixture appeared at the cut end of the flaps. The other pedicle of the flap was then divided, and roentgenograms were taken without opening the flaps.

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4. Fix in formaldehyde; bleach with hydrogen dioxide: wash in water twenty-four hours; dehydrate by passing through alcohols from 50 per cent to absolute; place in benzene (two changes); mount in methyl salicylate, U. S. P., 5 parts and benzyl benzoate 3 parts.

5. Spalteholz, W.: Ueber das Durchsichtigmachen von menschlichen und tierschen Präparaten, ed. 2, Leipzig. S. Hirzel, 1914.

6. Barium sulphate 1,000 Gm., powdered gelatin 300 Gm., distilled water 1,700 cc.

In both the first and second series of experiments, the entrance of the injection material into the flap was through a single pedicle, the upper pedicle being divided on one side and the lower pedicle on the other. This method was selected because the clinical utilization of pedunculated flaps necessitates the development of an adequate blood supply from a single pedicle before the flap can be implanted in a new location. The vessels demonstrated by the injection methods therefore represent the circulation which may be supplied by a single pedicle.

The third series of experiments made use of the flaps of the first series into which toluidine blue was injected. Sections were taken through the central portion of the flaps and stained with hematoxylin and eosin.

Fig. 1.—Typical opened, cleared specimen into which toluidine blue was injected and the flap removed immediately after its construction. Note the blood filled vessels crossing the flap at right angles to its long axis. Only the vessels immediately adjacent to the pedicle showed evidence of containing toluidine blue. Note that there were no vessels running parallel to the long axis of the flap.

RESULTS

With these three methods of study, the results may be summarized as follows:

Tubed flaps, removed immediately after their preparation showed blood-filled vessels crossing the flaps at right angles to their long axis. Only the vessels immediately adjacent to the pedicle showed evidence of toluidine blue within their lumen. There were no vessels running parallel to the long axis of the flaps.

Flaps removed at the end of one day showed a few vessels, filled with the injection mediums running almost the entire length of the flap. These vessels were more numerous at the region of the base of the flap, but there was a definite tendency for the long axis of the vessels to be parallel to the long axis of the flap.

At the end of four days, vessels containing the injection medium and running parallel to the long axis of the flap, were more marked.

Specimens removed on the seventh day showed what appeared to be a well developed blood supply, with vessels running from one end of the flap to the other.

Fig. 2.—Photomicrograph of a section taken through the center of a flap removed immediately after its construction. There are a moderate number of small and medium-sized blood vessels. There is marked hemorrhage in the center of the tubed flap with slight extravasation of blood into the subcutaneous tissue.

From the seventh to the fourteenth day there appeared to be little change in the number, character or size of the vessels.

The microscopic study of sections taken through the central portion of flaps of different ages may be summarized as follows:

On the day of operation there were a moderate number of small and medium-sized blood vessels and marked hemorrhage in the center of the tubed flap with slight extravasation of blood into the subcutaneous tissue.

On the first day a moderate number of small and medium-sized blood vessels were seen with diffuse extravasation of blood throughout the subcutaneous tissue and slight polymorphonuclear leukocytic infiltration.

On the fourth day there were small and medium-sized blood vessels, apparently more in number than on the first day, marked polymorphonuclear leukocytic infiltration in the cutis vera.

On the seventh day there were many small, medium and large blood vessels in the subcutaneous tissue and in the deeper portion of the cutis

Fig. 3.—*A*, typical opened, cleared specimen into which toluidine blue was injected and the flap removed after twenty-four hours. *B*, roentgenogram of a flap into which an opaque mixture was injected and the flap removed after twenty-four hours. A few vessels filled with injection material can be seen running almost the entire length of the flap. These vessels are more numerous at the region of the base, but there is already a definite tendency for the long axis of the vessels to be parallel to the long axis of the flap.

vera, and early granulation tissue in the cutis vera, containing many capillaries.

On the eleventh day many small, medium and large blood vessels were seen in the subcutaneous tissue and in the cutis vera; there was well developed granulation tissue in the cutis vera.

SUMMARY OF EXPERIMENTS

Injection experiments of tubed double pedicled skin flaps indicate the establishment of an adequate blood supply from a single pedicle within seven days. Histologic studies of these specimens support this conclusion.

The development of an adequate blood supply appears to be dependent on three factors: (1) an increase in the size of the vessels; (2) an increase in the number of functioning vessels, and (3) a reorientation of the main vascular channels corresponding to the long axis of the flap.

Fig. 4.—Types of roentgenograms of flaps into which an opaque mixture was injected and the flaps removed at the end of four days. The vessels containing the injection medium and running parallel to the long axis of the flap are more marked than in the one day specimens as shown in figure 3.

CLINICAL APPLICATION

In order to understand the clinical problem with which we are dealing, it may be advantageous to review the anatomy of the blood supply of the human skin.

The anatomy of the cutaneous blood vessels in man has been carefully described and illustrated by Spalteholz.[7] There is a marked

7. Spalteholz, W.: Die Verteilung der Blutgefässe in der Haut. Arch. i. Anat. u. Entwcklngsgesch., 1893, pp. 1-54.

variation in the number and size of the vessels to the skin in different regions of the body. The number is greater to those portions of the skin which are subjected to external pressure, such as the palms of the hands, soles of the feet and the gluteal region.

All branches of the arteries supplying the skin anastomose freely with each other and with neighboring vessels and form a cutaneous arterial network situated in the deepest layer of the cutis. The mesh of this network is smaller in the more vascular regions. From this, arched and branching vessels proceed outward, and anastomosing, form

Fig. 5.—*A*, cleared specimen into which toluidine blue was injected and the flap removed at the end of seven days. Compare this with the vessels shown in figures 1 and 3 *A* and note the vessels running the full length of the flap. *B* and *C*, roentgenograms of flaps into which an opaque mixture was injected and removal done at the end of seven days. These specimens show a well developed blood supply with numerous vessels running from one end of the flap to the other. Compare these with figures 3 and 4 and note the marked change in the size and number of the vessels and in the reorientation which has occurred.

a second subpapillary arterial network near the junction of the middle and outer thirds of the cutis.

Numerous small branches arise from the subpapillary network and run as terminal arterioles to the superficial layers of the skin. Most of these turn and course for a short distance parallel to the surface of

the skin, following, in the palm of the hand and the sole of the foot, the direction of the papillary ridges beneath which they run. They send their twigs to the arterial limbs of the capillary loops, lying in the papillae.

The venous blood, returning from the capillary loops in the papillae, passes through several networks. The first lies immediately beneath the bases of the papillae and receives blood from the venous limbs of the capillary loops and from minute collecting venules formed by the union of several such capillaries. Almost immediately beneath this is a second venous network, the two intercommunicating freely by short

Fig. 6.—Photomicrograph of a section taken through the center of a flap removed at the end of seven days. There are many small, medium and large blood vessels in the subcutaneous tissue and in the deeper portion of the cutis vera. There is also early granulation tissue in the cutis vera containing many capillaries. A comparison of this section with that in figure 2 is interesting as it shows the marked increase of blood vessels both in size and number which have developed in seven days.

venules; these two networks are often termed the subpapillary venous plexus. The blood flows deeper by numerous tributaries to a third and fourth venous network, the former lying immediately deep to the subpapillary arterial plexus, the latter at the level of the cutaneous plexus of arteries, where cutis and subcutis join.

The general arrangement of the vessels is illustrated in the diagram (fig. 9), modified from that originally published by Spalteholz.

Thomas Lewis,[8] in his monograph on the blood vessels of the human skin, utilized a somewhat less involved terminology in distinguishing the various vessels, classifying them as strong arterioles, minute vessels and deep veins.

The classification used by Lewis is much simpler than that prepared by Spalteholz. If detail is desired in descriptions the classification of Spalteholz is to be preferred, but for ordinary use that of Lewis is sufficient.

The results of the experimental work have been so significant, that although we have not had the opportunity of making injections into

Fig. 7.—Photomicrograph of a section taken through the center of a flap removed at the end of eleven days. There are many small, medium and large blood vessels in the subcutaneous tissue and in the cutis vera. There is also well developed granulation tissue in the cutis vera. There is not much difference in the development of the blood vessels shown in this section and that shown in the seven day specimen in figure 6.

flaps on human beings, we feel justified in surmising from clinical observations along the same line that much the same process takes place as in the animal experiments, and that in a tubed flap the normal vessels of the human skin also increase in size and number and that the

8. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

main vascular channels are reoriented to correspond to the long axis of the flap.

The information obtained from the animal experiments seemed worthy of a careful clinical tryout. This was checked at first on patients as follows. Tubed flaps which had been prepared for transplantation to definite defects were used. We started with the division of the pedicle on the fourteenth day and gradually reduced the time until now in suitable cases we sometimes divide the pedicle on the tenth day. However, we usually prefer to divide the selected pedicle piecemeal, that is, a third or half way through on the tenth and the

Fig. 8.—Typical roentgenogram of a flap into which an opaque mixture was injected and the flap removed at the end of fourteen days. There is little change to be noted in the vessels on comparison of the fourteen and the seven day specimens, either in number, character or size.

remainder on the eleventh or twelfth days, depending on whether the separation is done in halves or thirds, and have adopted this as a routine procedure in dealing with ordinary tubed flaps. Frequently there is definite arterial bleeding from the end of the tube when the pedicle is divided. This usually comes from near the central portion of the flap, but sometimes is well to one side or the other.

From the experimental data we might be justified in starting this division as early as the seventh or eighth day, but as yet we have not

chanced the loss of a portion of the flap by trying this out clinically
and think it safer not to begin the division of the first pedicle until
the tenth day (fig. 10).

If there is doubt in the mind of the operator as to the vitality of
the tube in any particular case, it is, of course, advisable to delay the
division for full two weeks, or as much longer as conditions require.
From the standpoint of the comfort of the patient, there is usually no
particular hurry in dividing the first pedicle. On the other hand, when
to divide the base pedicle, when the flap comes from a distant part,
say from the arm to the face, is a much more important matter to the
patient, on account of the enforced irksomeness of the position. We

Fig. 9.—Diagram showing the arrangement of the human cutaneous blood ves-
sels, Spalteholz' classification being used (Lewis). *A* and *B* indicate the subpapil-
lary venous plexus (*A*, the first venous plexus and terminal arterioles and *B*, the
second venous plexus) ; *C*, the subpapillary arteriolar plexus; *D*, the third venous
plexus; *E*, the epidermis; *F*, the cutis; *G*, the arched arterioles; *H*, the fourth
venous plexus; *I*, the sweat gland layer; *J*, the cutaneous arterial plexus.

have found that when the tube has been opened out for one-third its
length or more and has been sutured in close contact with its new
bed, that, all other conditions being favorable, we can begin to divide
the pedicle as early as the eighth or ninth day and have the arm down
on the tenth or eleventh day rather than wait two weeks as we had
previously done. In these cases there is often profuse bleeding from
both ends of the divided pedicle showing a good circulation originating
in this period of time from the new base, as well as from the original
source of blood supply.

Fig. 10.—The early division of pedicles and transference of a tubed flap from the arm to cheek. *A*, a tubed flap 13 cm. long formed on the inner side of the arm. This flap was planned in width, length and position to fill a defect to be made by the excision of a contracted scar of the cheek and lip. Note the complete formation of the tube, the type of pedicles and that the skin has been sutured beneath the tube. The lower pedicle was divided in stages beginning on the tenth day, and the division was completed on the eleventh day at which time the flap was opened for about half its length and was transferred and sutured, after raising the arm, into the defect on the cheek made by the excision of the contracted scar tissue and for which it had been prepared. *B* and *C*, the base pedicle on the arm was gradually divided beginning on the ninth day. Note the partial division in *B*. The division was completed on the tenth day. There was free bleeding from the stump attached to the cheek. This stump was opened and utilized. No portion of the flap was lost by the early division of either pedicle. *D*, the final result of the transfer of the tubed flap. Note the smooth normal looking skin which fits into its new environment quite naturally.

SUMMARY

The clinical application of the information obtained in this experimental study has been successfully tried out on tubed flaps during the last three years. It has also been of value in determining the time of division of the pedicles in those long pedicled flaps which are raised and without being tubed are immediately sutured back into the bed from which they came until ready for transfer.

The longer the tubed flap is allowed to remain intact, within certain limits, the more stable the blood supply becomes, but from our observations, both clinical and experimental, we are convinced that the establishment of circulation in tubed skin flaps occurs considerably earlier than was previously thought possible and consequently that it is safe to divide the pedicles sooner.

A PATH OF INFECTION IN PERINEPHRITIS

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Last year, before the Chicago Urological Society, Dr. Burstein and I reviewed a series of fifty-five cases of perinephritic abscess.[1] Thirty-two were metastatic in origin. The metastatic abscesses are of particular interest because they are usually diagnosed only when the condition has become well developed. They are, in the vast majority of cases, primarily cortical abscesses of the kidney,[2] thus accounting for the difficulty in their diagnosis. The abscess at first does not communicate with the renal pelvis, so that the urinary and pyelographic findings are negative until some weeks later, when the abscess has extended and communicates with the pelvis. The outer capsule undergoes inflammatory reaction and encapsulates the abscess, and thus here also evidence does not usually present itself until the abscess has spread into the perinephric tissue, when it is possible to make the diagnosis by the presence of a tumor, the finding of pus by aspiration or roentgenologic evidence.

The various modes of invasion in perinephritis are pictured in the accompanying diagram (fig. 1). One of the paths of extension of infection—that along the periureteral sheath, of which very little mention has been made in the literature—is here shown.

Since that report, I have operated in twelve cases of perinephritic abscess, one of which was bilateral. Two of these cases are of particular interest in that they indicate the path of infection as the sheath of the ureter. Other postoperative and postmortem observations are also of interest, for they show quite definitely the ureteral sheath as the pathway of infection from the pelvis upward and from the kidney down. These various observations prompted the experimental roentgenologic observations on postmortem specimens of kidneys, ureters and bladder, which will be reported. The various clinical observations will be briefly mentioned first.

REPORT OF CASES

CASE 1.—In a woman, five days after a normal labor, a chill developed, followed by a fever which persisted for weeks and which was septic. There were no pelvic or urologic findings. After six weeks some tenderness and rigidity in the right

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loin prompted incision of this region. A large perinephritic abscess, which had extended in sacculations from the pelvis up to the kidney, was drained. Six weeks later, a left perinephritic abscess was drained. This abscess also extended along the posterior part of the peritoneum from the base of the bladder up to the kidney.

CASE 2.—In a man aged 55, who gave a history and rectal findings of a chronic prostatovesiculitis, a septic temperature with some tenderness in the right lumbar region developed. Cystoscopic, urinary and roentgen findings were negative. A diagnosis of perinephritic abscess was made two weeks later by puncture and aspiration. At operation a large abscess, extending up to the kidney but lying in the dead space below it, was drained. Exposure of the ureter showed marked thickening and irregularity throughout its entire course from the bladder to the kidney.

Fig. 1.—Diagram to show sources of perinephritic abscess. *A,* hematogenous form, face of infection elsewhere in body; *B,* extension of perinephritic abscess to subphrenic space; *C,* extension of infection from cortical abscess of kidney to fat around it; *D,* same as *C,* but by way of lymphatics; *E,* retrocecal appendiceal abscess extending to perinephric fat, and *F,* extension of infection from prostate, etc., along periureteral sheath. (From Eisendrath and Rolnick: Urology, Philadelphia, J. B. Lippincott Company, 1930, p. 690.)

In the first case, the abscess may have developed and extended upward by continuity along the posterior peritoneum from the base of the bladder to the kidney. It may also have extended along the sheath of the ureter.

In the second case, the evidence at hand, the previous prostato-vesiculitis, with negative urinary findings, and the irregularity, thickening and beading of the ureter indicate extension along the sheath of the ureter. The abscess did not involve the perinephric tissue, for it

had most likely broken through the ureteral sheath at one or more points before extending to the kidney.

Case 3.—Ten days following a low ureterotomy for stone, the patient required exposure of the kidney of that side because of pain, tenderness and rigidity over the lumbar region, together with chills and fever. An abscess was found which was entirely subcapsular and had no renal involvement.

Here also the extension of the infection, undoubtedly from the site of the ureterotomy wound, was either along the lymphatics of the wall of the ureter or more likely along the sheath of the ureter.

Case 4.—Two days following a difficult nephrectomy in a case in which a small portion of the pelvis was left because it was bound down toward the median line very close to the vena cava, funiculitis of the spermatic cord of that side with some tenderness developed. This gradually subsided and cleared up completely when the patient left the hospital eighteen days following the operation.

Case 5.—A nephropexy for kink of the ureter, in which the ureter was freed from adhesions, was followed within thirty-six hours by a rather marked crepitus of air emphysema in the spermatic cord of the same side high up in the scrotum. There was no scrotal emphysema. The patient made an uneventful convalescence, the emphysema clearing up within six days.

Cases 4 and 5 indicate rather clearly the path of the funiculitis and the air emphysema of the spermatic cord as the sheath of the ureter and by extension at the junction of the ureteral sheath with that of the seminal vesicle along the sheath of the vas to the external inguinal ring. A few years ago, I demonstrated the possibility of infection along the sheath of the vas,[3] and also presented clinical evidence of the same. Abscess and funiculitis usually present themselves in the groin at Bogros's space,[4] a loose band of connective tissue separating the pelvic from the scrotal vas.

Case 6.—At operation for a transcapsular rupture of the kidney, a fairly marked hematoma was present; blood had also extravasated along the posterior peritoneum downward for some distance along the sheath of the ureter.

Case 7.—Autopsy in a man who had a marked pelvic infection disclosed a calculus in the cavity of a prostatectomy wound of a year before. This had eroded through the prostatic capsule. The inflammatory involvement extended downward along the sheath of the vas up to the scrotal portion and also upward along the sheath of the ureter and posterior peritoneum up to the perirenal tissues.

These various observations of extension of infection from the pelvis upward and from the kidney downward, with no associated urinary findings, as shown in the first five cases, indicate the path of infection as

3. Rolnick, H. C.: Infections Along the Sheath of the Vas Deferens, J. Urol. **14**:371 (Oct.) 1925.

4. Belfield, W. T., and Rolnick, H. C.: Roentgenography and Therapy with Iodized Oils, J. A. M. A. **86**:1831 (June 12) 1926.

along the outer wall of the ureter or its sheath. The rapid extension
downward of pus and air to the spermatic cord and of blood along the
sheath of the ureter is strong evidence of extension of the process along
the sheath of the ureter and by continuity along the sheath of the vas.

Considerable experimental work has been done on ascending infec-
tion of the kidney. Eisendrath and Schultz [5] showed that infection may
extend upward along the anastomotic chain of lymphatics in the wall of

Fig. 2.—Postmortem specimen of bladder, ureter and kidney; the peritoneum is
still attached to the ureter. The periureteral sheath is shown with injection of
contrast medium throughout most of its length.

the bladder and ureter, and that ascending infection can develop in this
manner secondarily from infection of the prostate and seminal vesicle.

Belfield,[6] in his classic paper on "Pus Tubes in the Male," described
the intimate relation of the ureter, vesicle and vas as the broad ligament

5. Eisendrath and Schultz: J. M. Research **35**:295 (Jan.) 1917.

6. Belfield, W. T.: Pus Tubes in the Male, J. A. M. A. **53**:2141 (Dec. 25)
1909.

in the male and showed the close proximity of the fascia and sheath of the seminal vesicle with that of the ureter.

Von Lichtenberg [7] discussed pathologic involvement of the upper urinary tract secondary to adnexal disease in the male and showed varying degrees of hydronephrosis and renal infection resulting therefrom, some cases even requiring nephrectomy. These all resulted from compression of the lower part of the ureter by the seminal vesicle and stric-

Fig. 3.—Postmortem specimen of bladder, ureter and kidneys; contrast fluid is shown injected into both ureteral sheaths extending from the base of the bladder up almost to the kidney.

ture of the ureter, owing to extension of infection to the ureter from the prostate and seminal vesicles.

Considerable emphasis has been given of late to the importance of adnexal disease in the male in pathologic involvement of the upper urinary tract. Von Lichtenberg [7] spoke of the junction of the urinary and genital tracts in the male at the point where the vas crosses the

7. von Lichtenberg: J. Urol. 24:1 (July) 1930.

ureter and the seminal vesicle comes in contact with the ureter as a
bad corner. At this point, there is a common nerve, blood and lymph
supply. The ureteral sheath communicates here with that of the seminal
vesicle and also with the loose fascia at the base of the bladder in both
males and females.

The sheath of the ureter covers the ureter along its entire course,
extending upward from the base of the bladder, enveloping the renal

Fig. 4.—Various specimens showing the injection of the periureteral sheaths
with contrast fluid at various points along their course.

pelvis and infiltrating and covering the fatty and true renal capsule.
Within this sheath the ureter has considerable of its blood, lymph and
nerve supply. In performing a ureterotomy for stone, it is best to leave
the ureter attached to the peritoneum. Traction on the ureter and
separation from the peritoneum may result in separating it from its
sheath. Slough of the ureter and persistent fistulas may result from
depriving it of its blood, lymph and nerve supply. It is, therefore, evi-
dent that the ureteral sheath is an important structure, and that it also
permits possible extension of infection.

The periureteral sheath is also considered in Eisendrath and Rolnick's [5] "Urology" as a path of extension of infection to the perirenal tissue from the parametria, prostate, seminal vesicles and bladder.

EXPERIMENTAL DATA

The experiments for the purpose of determining the accuracy of the various clinical observations were made as follows:

Fig. 5.—Specimen showing the injection of the periureteral sheath of each side with contrast fluid practically its entire length.

Fresh postmortem specimens of both kidneys, ureters and bladder were employed. The specimens were from both males and females, children and adults; in all, thirty were obtained over a period of a few months. In the male the adnexae were also attached.

A contrast fluid of from 25 to 30 per cent sodium bromide solution was injected into the ureteral sheath, and the specimen was then roentgenographed. Injections were begun either in the fascia at the base of the bladder near the ureter or within

8. Eisendrath, D. N., and Rolnick, H. C.: Urology, Philadelphia, J. B. Lippincott Company, 1930, p. 689.

the sheath of the seminal vesicle. In others, injection was made directly into the ureteral sheath, beginning at the juxta vesicular portion of the ureter and extending upward. In a few specimens the injections within the sheath were begun at the renal pelvis and carried downward. In practically all instances, the contrast fluid could be forced very readily upward or downward along the sheath of the ureter. In the female, infiltration of the loose tissues at the base of the bladder permitted the forcing up and milking upward of the contrast medium in the ureteral sheath. The accompanying illustrations (figs. 2, 3, 4, 5 and 6) show the ureteral sheath into which contrast fluid was injected in the various ways mentioned.

Fig. 6.—In each of these specimens, pyelograms and ureterograms have been made of one side to show the contrast with the other side in which injection into the ureteral sheath has been made. On the left hand side injection has been made into the ureteral sheath, from the base of the bladder upward. Air has been injected into the lumen of the ureter. On the right hand side, a ureteral catheter has been inserted into the lumen of the ureter, and injection made into the ureteral sheath from the bladder upward.

COMMENT

This, I believe, is the first time that the possibility of extension of infection along the sheath of the ureter has been demonstrated roentgenographically. These clinical and experimental observations should be of particular interest to gynecologists as well as to urologists. There are many clinical observations by both gynecologists and urologists of adnexal and pelvic infection causing infection of the upper urinary tract.

The demonstration of extension of infection along the sheath of the ureter is of decided clinical importance.

Bands and adhesions about the ureter and renal pelvis, periureteritis, peripyelitis and perinephritis, acute and chronic and of varying degrees of severity, including perinephritic abscess, may result from extension of infection along the sheath of the ureter secondary to pelvic infection in both male and female.

RESECTION OF SENSORY NERVES OF PERINEUM IN CERTAIN IRRITATIVE CONDITIONS OF THE EXTERNAL GENITALIA

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The purpose of this paper is to form some estimate of the efficacy of neurectomy of sensory nerves in the treatment of certain irritative lesions of the female external genitalia. The intolerable itching which may be associated with such conditions as kraurosis, leukoplakic vulvitis and pruritus of the vulva with or without lichenification is often particularly resistant to local medication, whether this consists in the application of drugs or in exposure of the region to roentgen or actinic rays. This distressing symptom not only leads to excoriation of the parts, but also reduces the physical and moral stamina of the patient by depriving her of sleep. Two surgical procedures are available for the treatment of these conditions: vulvectomy and section of the sensory nerves to the parts. The choice of operation may be simplified by the occasional appearance of malignant lesions in the course of one of these diseases, a matter that has been recently dealt with by one of us;[1] in such cases either simple or radical vulvectomy, according to the degree of malignancy, is obviously the correct treatment. In cases in which there is not any suspicion of malignant degeneration, section of the sensory nerves of the area avoids the element of mutilation inseparable from vulvectomy. At first sight it would appear that neurectomy is merely symptomatic treatment; however, we have evidence that this operation may have a healing effect on the cutaneous lesions. This evidence, with a description of the histologic appearance of the skin before and after operation, will be presented in a subsequent paper.

THE NERVES OF THE EXTERNAL GENITALIA

The pudic nerve (fig. 1) is derived chiefly from the third and fourth sacral segments of the spinal cord, and also receives a small contribution

1. Counseller, V. S.: Leukoplakic Vulvitis or Kraurosis Vulvae; Its Relation to Carcinoma and Its Surgical Treatment, Minnesota Med. **14**:312 (April) 1931.

from the second sacral segment. It enters the ischiorectal fossa around
the lower border of the small sacrosciatic ligament, and runs on the
inner aspect of the obturator internus muscle in a fascial tunnel known
as Alcock's canal. At first it has the pudic artery and veins on its outer
side, but soon takes up a position superficial to these vessels. Soon after
its appearance in the fossa it gives off its inferior hemorrhoidal
branches, which cross the space to supply the posterior part of the

Fig. 1.—The anatomy of the pudic nerve (Spalteholz).

external anal sphincter and the skin overlying this; not uncommonly,
however, these branches arise directly from the sacral plexus and enter
the fossa separately. The trunk itself courses forward and becomes
more superficial; it ends by dividing into the perineal nerve and the
dorsal nerve of the clitoris. Sometimes the trunk divides into these
in the posterior part of Alcock's canal; sometimes its final division is
delayed until it reaches the superficial transverse muscle; usually the
separation into its terminal branches takes place about the middle of

Alcock's canal. Wherever they are formed, the perineal nerve lies superficial to the pudic vessels, and the dorsal nerve of the clitoris deep to them.

The perineal nerve almost at once divides into two branches: superficial and deep. The superficial perineal nerve is purely sensory, and passes forward to divide into the external and internal labial nerves, which may be traced at least as far as the middle of the labia majora; the external nerve usually goes superficial to the transversus perinei muscle, the internal nerve through or deep to that muscle. The external labial nerve anastomoses with the pudendal branch of the small sciatic nerve. The first offshoot of the deep perineal nerve is a branch for the anterior part of the sphincter ani externus. When the pudic nerve divides about the middle of Alcock's canal, this anal branch passes transversely to its destination; on the other hand, when the final division of the pudic nerve is delayed until it reaches the posterior border of the superficial transverse muscle, the anal branch curves backward and somewhat inward to reach the sphincter. The uncertainty of the course pursued by the anal nerve makes it necessary for the surgeon to identify and avoid it during resection of the sensory nerves of the area. The deep perineal nerve then leaves the fossa by passing deep to the superficial transverse muscle and between the two layers of the triangular ligament; it is expended chiefly in the supply of the muscles in the anterior part of the perineum: the superficial transverse muscle, the posterior part of the constrictor urethrae,[2] the ischiocavernosus and the sphincter vaginae; it also sends branches to the bulb of the vestibule.

The dorsal nerve of the clitoris passes between the two layers of the triangular ligament, in company with the pudic artery; in this part of its course it gives motor fibers to the anterior part of the constrictor urethrae. Close to the symphysis it pierces the triangular ligament and ends in the supply of the clitoris.

The small sciatic nerve, which is derived from the first, second and third sacral nerves, also contributes to the sensory innervation of the external genitalia. One of its descending branches, the pudendal branch, runs mesially and forward, and courses toward the vulva about 2 cm. lateral to the ramus of the ischium. Finally, it pierces the deep fascia, and after anastomosing with the external labial nerve, it is distributed to the posterior half of the labium majus, and to the adjacent part of the skin of the perineum.

The anterior third of the labium majus derives its sensory supply from the terminal branches of the ilio-inguinal nerve and the genital

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2. Including that part of this muscle sometimes separately described as the transversus perinei profundus.

branch of the genitocrural nerve. The ilio-inguinal nerve is derived from the first, and the genitocrural from the first and second lumbar segments of the spinal cord.

The cutaneous areas subserved by each of the main sensory nerves are shown in figure 2, which has been modified from Tavel.[3] On account of the rich anastomosis between their terminal twigs, the area supplied by each nerve is not sharply demarcated, and as a corollary the division of any one of them does not lead to complete paralysis of sensation in the territory attributed to it. This is especially the case with the labial nerves, the fine terminal branches of which often appear to overlap the field of the ilio-inguinal and genitocrural nerves. However, sensation

Fig. 2.—The cutaneous distribution of the nerves of the perineum in the female (modified from Tavel) : *a*, ilio-inguinal and genitocrural nerves; *b*, dorsal nerve of clitoris; *c*, superficial perineal nerve; *d*, pudendal branch of small sciatic nerve, and *e*, inferior hemorrhoidal nerve.

in the posterior two thirds of the labia majora may be greatly blunted by division of the superficial perineal nerves and the pudendal branches of the small sciatic nerves; the clitoris may be added to this area by division of its dorsal nerves.

From an analysis of the sensory innervation of the perineum, it will be apparent that in order to allay irritation about its hinder part, the surgeon should aim at dividing the superficial branches of the perineal

3. Tavel, E.: La résection du nerf honteux interne dans le vaginisme et le prurit de la vulve, Rev. de chir. **25**:145, 1902.

nerves, the pudendal branches of the small sciatic nerves and, if neces-
sary, the dorsal nerves of the clitoris. The muscular branches of the
deep perineal nerves to the anterior part of the sphincter ani must be
carefully preserved; the nerves to the posterior part of the sphincter ani
are not likely to be displayed during the operation.

TECHNIC OF OPERATION

For seventy years sporadic reports of operations on the pudic nerves have
appeared in surgical and gynecologic literature. Most of these reports attribute
the first operation to Sir James Y. Simpson [4] of Edinburgh, but give a reference
to one of his papers which does not allude to neurectomy. The correct reference [4]
contains a description of the procedure, under the heading "Hyperaesthesia and
Neuralgia of the Vulva," and gives priority in its use to Dr. Burns of Glasgow.
This description is quoted to show the first step in the evolution of the operation.
It may be added that the temporary nature of the results obtained by the original
method were obviously due to regeneration of the nerves.

"There is one other morbid condition of the female genital organs, regarding
which you must allow me to say a word or two during the few minutes we have
still at our disposal. It is observed chiefly in married women who come to you
complaining that contact with a certain point in the sides of the vaginal orifice, or
vulva, causes them such acute suffering that they are totally unable to endure any
attempt at marital intercourse. This pain seems to be due to a state of hyper-
aesthesia of the pudic nerve, and was first described by Dr. Burns, of Glasgow, who,
in his Principles of Midwifery, after describing the anatomical distribution and
relations of the nerve, goes on to say that it 'is often preternaturally sensible, so
as to cause great pain in coitu, as well as at other times. It may be exposed, by
cutting through the skin and fascia, at the side of the labium and perineum; begin-
ning on a line with the front of the vaginal orifice, and carrying the incision back
for two inches. The nerve being blended with cellular substance is not easily seen
in such an operation; but it may be divided by turning the blade of the knife, and
cutting through the vagina to its inner coat, but not injuring that. It may be more
easily divided by cutting from the vagina. Slitting, merely, the orifice of the vagina
will not do; we must carry the incision fully half an inch up from the orifice, and
also divide the mucous membrane freely in a lateral direction.' I formerly knew
one or two patients who had consulted Dr. Burns in regard to this affection, and in
whom the pudic nerve had been divided in the manner he describes, either by
himself or by his son; yet in these patients the painful sensation returned, though
sometimes not in the same place, but in the track of some other nerve. I believe,
with Dr. Burns, that the best palliative treatment for such cases is division of the
affected nerve; but, instead of laying it bare, I have usually cut it through sub-
cutaneously, by means of an ordinary tenotomy knife. It is a surgical measure far
more simple in its character. Occasionally there is greater supersensitiveness
and neuralgia of the vulva and vaginal orifice, without there existing any
local lesion whatever capable of accounting for it. The pain is not then usually
limited to any one single point. Such cases require the usual constitutional treat-
ment of neuralgia, as iron, manganese, arsenic, etc., sometimes in long-continued

4. Simpson, J. Y.: Clinical Lectures on the Diseases of Women: Lecture 10.
On Caruncles of the Urethra—Neuromata of the Vulva—Hyperaesthesia and Neu-
ralgia of the Vulva, M. Times & Gaz. **39**:333 (April 2) 1859.

courses. You have to use general anti-neuralgia tonic medicines and measures; and locally all forms of sedatives and anodyne applications."

Alternative methods for resecting the nerves of the perineum have been described by Rochet [5] and Tavel, and recently by Wertheimer and Michon.[6] It is possible to approach the resection by either of two plans: by finding the trunk of the pudic nerve, and then tracing it peripherally to the desired branches, or by finding certain peripheral branches and tracing them proximally to the terminal branches of the trunk. In our experience the second method has proved satisfactory (figs. 3 and 4).

The patient is placed in an exaggerated lithotomy position, and the parts are prepared. The steps of the operation are the same on both sides. The length of the incision varies from 7.5 to 10 cm., depending on the obesity of the subject. It is placed parallel to and about 3 cm. from the rami of the ischium and pubis, about

Fig. 3.—Division of nerves of vulva, first stage. Inset, the incisions.

five sixths of it being anterior to the anus. An incision so placed rarely gives rise to subsequent discomfort in walking or sitting. The incision is deepened by blunt dissection until the posterior border of the superficial transverse muscle is reached. The superficial perineal packet of vessels and nerves is then isolated as it turns forward around the muscle. It is not unusual for this packet to contain only the inner of the two labial nerves; the outer labial nerve should then be sought as it turns around the border of the muscle. We have not found it of any advantage to attempt to preserve the small arteries and veins in the packet; it is divided between two clamps. The outer nerves in the grasp of the distal clamp are then traced distally, in an attempt to find their anastomosis with the pudendal branch

5. Rochet, V.: Traitement chirurgical des prurits périnéaux, anaux et vulvaires, Lyon méd. **100**:570, 1903.

6. Wertheimer, P., and Michon, L.: La névrotomie du nerf honteux interne: indications, technique, résultats, J. de chir. **31**:497 (April) 1928.

of the small sciatic nerve; if the latter is reached it is divided and its distal portion is twisted out. If it is not reached, the labial nerves and vessels are ligated as far forward as possible, or twisted out, and the tissues thus isolated are removed. The nerves in the grasp of the proximal clamp are then traced proximally until the perineal branch of the pudic nerve is reached. The twigs of this nerve that run to the anal region are carefully safeguarded; if it is necessary to denervate the skin of this area, each terminal twig must be tweaked; only the twigs that depress the skin when tweaked are to be resected. The branches between the perineal nerve and the proximal clamp are removed, after ligation of any vessels. In this way a segment of the labial nerves from 5 to 8 cm. long may be resected, and a segment from 2 to 3 cm. long of the sensory branches of the perineal nerve to the skin around the anus.

Fig. 4.—Division of nerves of vulva, second stage.

If the dorsal nerve of the clitoris is to be resected, it may be found deep to the pudic artery, by following the perineal nerve (or bundle of nerves) toward the pudic trunk on the surface of the obturator internus muscle. Alternatively, if the division of the pudic nerve has taken place in the posterior part of its course, the dorsal nerve of the clitoris may be sought directly in Alcock's canal.

If it has been impracticable to isolate the pudendal branch of the small sciatic nerve in front, an attempt may be made to find the branch as it approaches the perineum. It runs parallel to and about 2 cm. to the outer side of the ramus of the ischium, and may be sought in this situation after retraction of the outer lip of the wound.

The deep layers of the wound are then approximated by a few points of catgut, and the incision in the skin is closed. We have not found it necessary to employ drainage. A similar procedure is then carried out on the opposite side. The postoperative treatment does not differ from that of any other operation on the perineum.

Two cases have been recorded by Rochet: [5]

A woman, aged 48, had pruritus for more than ten years; even the vagina and the urethra itched. Apparently the trunk of the pudic nerve was divided on both sides; the pudic vessels were preserved. The itching was relieved for at least three years.

A man, aged 50, had pruritus of the anus and scrotum for two years. The superficial branches of the perineal nerve, its branches to the skin around the anterior part of the anus and the pudendal branch of the small sciatic nerve were divided on both sides. The patient was completely relieved, and the cure persisted for at least eight months.

One case has been recorded by Murard: [7]

A woman, aged 54, underwent subtotal hysterectomy in 1922, under spinal anesthesia. A day or two after the operation she began to have symptoms of two distinct types: a feeling of weight in the perineum, with a sensation of fulness in the bladder leading to frequency, and pruritus of the vulva. Seven years after the original operation, the pudic nerves were divided on both sides. Five weeks later the pruritus had disappeared, and the parts appeared healthy. The presence of the perineal scars gave rise to a little inconvenience in walking Murard was of the opinion that an injury to the roots of the cauda equina during the administration of the spinal anesthetic was the exciting factor in the case, but in the discussion which followed its presentation, Basset stated that an analysis of a large series of cases in which spinal anesthesia was used did not lend support to this view.

One case has been recorded by Mauclaire: [8]

A woman, aged 34, two months after a pelvic operation, began to suffer from intense vulvovaginal pruritus, much pelvic pain and some vaginismus. At a second laparotomy, adhesions were separated and the remaining ovary was partially resected. The pruritus became worse. Eight months after the original operation, the right dorsal nerve of the clitoris **and** the left perineal nerve were resected. The patient was relieved of her symptoms, except that some vaginismus persisted.

One case has been recorded by Albertin: [9]

A woman had,suffered for eight years from pain in the bladder and vulvovaginal pruritus. On the right side the resection was limited to the perineal nerve, and on the left side the pudic nerve and artery were resected. The pruritus was relieved for the forty-five days the patient remained under observation. It is noteworthy that, after the neurectomy, the passage of a catheter could still be felt.

One case has been recorded by Tavel: [3]

A woman, aged 48, had suffered for a number of years from pruritus of the vulva, and an extreme degree of vaginismus. On the right side the perineal nerve

7. Murard, Jean: Troubles vaso-moteurs et hyperesthésiques consécutifs à une rachianesthésie.   Traitement par névrotomie des honteux internes, Bull. et mém. Soc. nat. d. chir. **55**:1153 (Nov. 6) 1929.

8. Mauclaire, P.: A propos du prurit vulvaire traité par le névrotomie bilatérale des nerfs honteux internes, Bull. et mém. Soc. nat. d. chir. **55**:1210 (Nov. 30) 1929.

9. Albertin: Résection des nerfs honteux internes, Lyon méd. **100**:572, 1903.

was avulsed, its anal branch being preserved; on the left side the perineal nerve was avulsed in its entirety. Three months later the patient was entirely relieved, but had a little trouble in retaining a liquid stool.

One case has been recorded by Bérard and Wertheimer: [10]

A woman, aged 52, had had intense pruritus of the vulva for fifteen months. This resisted local treatment and periarterial sympathectomy of both internal iliac arteries. The perineal branch of the pudic nerve was divided on both sides. The result was excellent; not only was there symptomatic relief, but the cutaneous lesions were much improved. Two years later the patient had a mild recurrence of itching, which yielded to rest in bed.

CASES OBSERVED AT THE MAYO CLINIC

CASE 1.—A woman, aged 45, came to the clinic on Oct. 31, 1930, complaining of itching of the vulva which had begun in 1928, after panhysterectomy. The patient had not obtained satisfactory relief from local applications. About the clitoris, and between the fourchet and the anus, were several rough and elevated whitish patches. The vulva was markedly atrophied. A diagnosis was made of kraurosis of the vulva and beginning leukokeratosis near the fourchet.

On November 13, a specimen of skin was removed immediately posterior to the fourchet. Thereafter both branches of the superficial perineal nerve were divided, on both sides, at the posterior border of the superficial transverse muscle; the pudendal branch of the small sciatic nerve was also divided on both sides. On December 1, the wounds had healed, after some drainage from the wound on the left. The patient expressed herself as completely relieved. Two days later a dermatologist assessed the decrease in leukokeratosis at 75 per cent. On Jan. 9, 1931, the patient's family physician wrote that the vascularity of the tissues was much increased, and that the itching had disappeared entirely. An area 1 cm. in diameter to the left of the clitoris was still white and caused discomfort at times. In December, 1931, the patient was well pleased with the result of the operation.

The tissue removed showed the histopathologic picture of leukoplakia.

CASE 2.—A woman, aged 49, came to the clinic on Nov. 28, 1930, complaining of intense itching of the vulva of four years' duration. This had resisted treatment by local measures. On the inner aspects of the labia majora the skin was thick and white, and showed numerous excoriations at their upper angle. The labia minora were absent. There was relatively little atrophy of the skin, the latter being for the most part thick, white and soggy. A diagnosis was made of pruritus of the vulva, which some authorities would possibly term kraurosis in the hypertrophic stage.

On December 4, the perineal branches of the pudic nerve were divided on both sides. The pudendal branch of the right small sciatic nerve alone was divided; that of the left nerve was not identified. A portion of skin was removed for examination. On December 19, itching was still felt at night. A small area of soggy skin was still present around the clitoris. On Feb. 16, 1931, some itching was still present on the right side. On Jan. 13, 1932, the patient reported that she had had little relief from the operation, and that the presence of the perineal scars somewhat interfered with walking.

Sections of the skin removed at the operation showed the histopathologic picture of kraurosis of the vulva in its hypertrophic stage.

10. Bérard, L., and Wertheimer, P.: Kraurosis vulvae. Névrotomie des nerfs honteux internes. Guérison, Lyon chir. **23**:524, 1926.

CASE 3.—A woman, aged 61, came to the clinic on Feb. 28, 1931, complaining of itching about the anus and vulva, of nine years' duration. This had been treated elsewhere by injections of alcohol about the anus and external genitalia, but without success. The vulva was edematous and swollen. The mucous membrane was blanched, and there was a small area of necrosis and sloughing on the inner aspect of one labium majus. The skin on the inner aspects of both thighs was mildly irritated. The perianal skin showed similar but less severe lesions. A diagnosis was made of kraurosis of the vulva and anus, and leukoplakic vulvitis with lichenification and abrasions.

On March 4, the perineal nerve on the right side was divided, including a branch to the skin around the anus, and a similar resection was performed on the left side. The pudendal branches of the small sciatic nerves were not divided. A small piece of skin was removed for examination. On March 25, the vulva was less gray and more pinkish. There was not any evidence of scratching or leukoplakia. On June 1, scratch marks and erythema were both absent. The vulva had the usual light pink tint seen in older life. The patient was completely relieved of the itching.

The skin from the vulva showed the microscopic features of both kraurosis and leukoplakia.

CASE 4.—A woman, aged 49, came to the clinic on June 29, 1931, complaining of intense itching about the vulva, of thirteen years' duration; at times this had been so intense that the parts had been scratched until they were raw. Local treatment had not been of any avail. She had had some trouble in controlling the rectal sphincter. A diagnosis was made of pruritus of the vulva, with slight kraurosis, and mild prolapse of the rectum.

On July 8, the neurovascular packet containing the right superficial perineal nerves and vessels was divided. On the left side the vessels were dissected from the nerves, and only the latter were resected. During the dissection the right pudic artery was wounded and had to be tied, and the trunk of the right pudic nerve was also divided. A small piece of skin was removed for histologic study.

On July 20, the patient was relieved of the itching. She still had some trouble in controlling the rectal sphincter. On August 25, she reported that she had complete relief from itching; the rectal trouble persisted. On Feb. 5, 1932, she reported that the operation had been "a perfect success."

The skin from the vulva showed the histopathologic picture of neurodermatitis.

CASE 5.—A woman, aged 55, came to the clinic on July 9, 1931, complaining of itching of the vulva of thirteen years' duration. Local treatment had not resulted in improvement. Around the vulva and anus there were pigmentation, excoriation and definite atrophy involving the inner aspects of the thighs as well as the vulvar folds. Patches of superficial ulceration were present in these areas. A diagnosis was made of kraurosis of the vulva.

On July 24, an ulcerated area near the clitoris was removed for histologic examination. Thereafter the superficial perineal branches of the pudic nerve and the pudendal branch of the small sciatic nerve were resected on both sides. On August 8, the patient was completely relieved of itching. On Jan. 16, 1932, she reported that her condition was greatly improved; a little itching about the urethra was still present, at night only.

The portion of skin removed showed the histopathologic picture of leukoplakia.

CASE 6.—A woman, aged 40, came to the clinic on Aug. 27, 1931, complaining of itching of the vulva of ten years' duration. The first lesions had appeared on the inner aspect of the right thigh. After various local measures had been tried,

a series of applications of radium was made (elsewhere) over the vulva. The labia majora were edematous and red. Their skin was atrophic and contained numerous telangiectatic vessels. Above the clitoris were several moderately deep crusted ulcerated lesions, involving both labia. A diagnosis was made of pruritus and actinodermatitis of the vulva.

On September 1, the superficial perineal nerves and the pudendal branch of the small sciatic nerve were divided on both sides. On September 15, the itching had disappeared. In spite of their unfavorable situation both wounds had healed by primary union. On Jan. 12, 1932, the patient reported that she was in excellent condition and had no itching, and that all the ulcerated areas had remained healed. A biopsy was not performed in this case.

CASE 7.—A woman, aged 55, came to the clinic on Aug. 11, 1931, complaining of itching of the vulva of four years' duration. A diagnosis was made of kraurosis, involving the labia minora and clitoris.

On August 19, a specimen was removed for histologic examination; the superficial perineal nerves and the pudendal branch of the small sciatic nerve were resected on both sides. On September 2, the only itching area remaining was a small patch near the clitoris, where skin had been removed. On September 17, the patient reported that there had been some discharge from both wounds. On November 2, a further report stated that the itching had almost completely disappeared. In January, 1931, the patient reported that she had periods of itching about three times in each twenty-four hours.

The skin removed at operation showed the histopathologic picture of kraurosis of the vulva.

FUNCTION AFTER OPERATION

The Depth of Sensory Paralysis.—It has been pointed out that the sensory supply of the female genitalia is not demarcated in strict zones, so that an accurate assessment of the sensory changes which result from neurectomy is difficult. We have found that the area of blunting of sensation corresponds fairly closely to the territory assigned in figure 2 to the perineal nerves, although an attempt has not been made to separate their territory from that of the pudendal branches of the small sciatic nerves. In one of our successful cases tactile sensibility was not absent, although it was somewhat depressed, the principal change observed being analgesia, graded —2 to —3 on a basis of 4. Although single, this is an interesting physiologic observation, for elsewhere in the body the division of a sensory nerve usually produces more extensive anesthesia than analgesia. As a corollary it is of interest that the irritation which is called itching was suppressed in an analgesic area, although touch could still be felt; the orthodox view appears to be that itching is felt by way of tactile fibers. We were unable to detect any such dissociation of anesthesia in our remaining cases.

The Control of the External Sphincter of the Anus.—The posterior fibers of the external anal sphincter receive their motor nerves through the inferior hemorrhoidal branches, the anterior fibers from the perineal branches. The preservation of the inferior hemorrhoidal nerves is scarcely a matter for concern, because they do not hamper the operator

and indeed may not appear in the field. More care is necessary to preserve the muscular branches to the anus that are derived from the perineal nerve; they were divided on one side in Tavel's case, without any gross loss of rectal control. Division of the trunks of the pudic nerves distal to their inferior hemorrhoidal branches would leave the motor nerves to the posterior half of the sphincter intact, and in these circumstances it is likely that the combined action of the smooth internal sphincter and the posterior half of the external sphincter would assure control, except of liquid stools and after the administration of purgatives.

The Control of the Constrictor Urethrae.—In women the striated muscle fibers surrounding the urethra lack the purposive arrangement

Fig. 5.—Normal cystometrogram, after division of the right pudic nerve and the left superficial perineal nerve: *a*, first appreciation of cold; *b*, first desire to void; *c*, first feeling of pain, and *d*, severe pain.

found in men. For the most part, they are set irregularly among the smooth muscle fibers that surround the wall of the tube. A part of this striated system is sometimes separately described as the transversus perinei profundus, and has assigned to it a function comparable to that of the external sphincter in men. This part of the sheet of striated muscle that closes the pelvic outlet in its anterior half can scarcely function as a true sphincter, because its fibers pass only behind the urethra, and form a sling for it rather than a circular controlling muscle.

The sheet of striated muscle fibers around the urethra receives motor nerves from the deep branch of the perineal nerve and from the dorsal nerve of the clitoris, the territory of the latter nerve being anterior to

that of the former; although its arrangement in the female is not mechanically adapted to function as a sphincter, the question of control of the bladder after operations on the pudic nerves is naturally of great importance. When the resection is limited to the purely sensory superficial perineal branches this question does not arise, but when it is desirable to divide the deep perineal branch and the dorsal nerve of the clitoris the surgeon must be able to assure his patient that the operation will not be followed by vesical incontinence. This sequel has not followed neurectomy, either in our hands or in those of others; evidently, in women, the smooth sphincter is sufficient to provide, not only for retention of the urine, but for its periodic evacuation. If any branches of the pudic nerves played an essential part in vesical control, incontinence of urine ought to have followed operation in our case 4, in Rochet's case 1, in Murard's case, in Mauclaire's case and in Albertin's

Neurectomy of Perineal Nerves

Observer	Patient Observed; Time	Result
Rochet	3 years	Completely relieved
Bérard and Wertheimer.	2 years	Slight temporary recurrence after two years
Learmonth	14 months	Almost completely relieved
Learmonth	13 months	Little, if any, relief
Rochet	8 months	Completely relieved
Learmonth	7 months	Completely relieved
Learmonth	6 months	Almost completely relieved
Learmonth	4 months	Completely relieved
Learmonth	4 months	Almost completely relieved
Learmonth	3 months	Completely relieved
Tavel	3 months	Completely relieved
Albertin	7 weeks	Completely relieved
Murard	5 weeks	Completely relieved
Mauclaire	Not stated	Relieved of pruritus; some vaginismus persisted

case. In our case 4, a normal cystometrogram was obtained after the operation (fig. 5).

CONCLUSIONS FROM RESULTS OF OPERATIONS

The results of the fourteen operations reviewed in this paper are best tabulated according to the period during which the patient remained under observation (table).

Experience has shown that the immediate effect of operation is to banish the pruritus. This desirable result has been absent in only one case (our case 2). We have not been able to explain this failure, as a result either of difficulty in performing the operation, or of any peculiarity of the vulvar lesion; it must be accepted as a failure. Granted that immediate relief is the rule, it is obvious that the permanence of relief depends on the possibility of regeneration in the severed nerves; therefore, only the first four cases in the table are of value in assessing the late results of operation. In case 1 the result might well be called permanent. In case 2 the possibility arises that the recurrence after the elapse of

two years was due to the restoration of additional sensibility to the skin, although the temporary nature of the recurrence is against this view. In case 3, the interval since operation is scarcely long enough to permit labeling the result permanent. In case 4 the result was a failure from the first. In the remaining ten cases, assessment of the immediate relief alone can be made; this was satisfactory in all.

It follows that every care must be taken at operation to resect or twist out sufficient lengths of the desired nerves to reduce the likelihood of restoration of their continuity. In their course the superficial perineal nerves undergo a sharp change in direction, and moreover their origin from the perineal nerve is on a substantially deeper plane than is their cutaneous distribution. It appears to us that the restoration of any considerable degree of innervation is unlikely in the territory of the labial nerves. It is otherwise for the nerves supplying the skin anterior to the anus. Their direction and plane correspond to those of the parent nerve, and it is not possible to resect more than a short segment of them; to guard against regeneration, the parent branches may be doubled back and tied in this position.

The operation appears to be well borne. Two patients in the complete series complained that the perineal scars interfered with walking; in one of these (our case 2) the operation had been totally ineffective, and in the other (Murard's case) the surgeon was unable to detect any alteration in the gait of the patient. We have indicated that a carefully performed operation does not prejudice the function either of the bladder or of the rectum.

To sum up, we feel that neurectomy may well be offered to patients suffering from irritative conditions of the vulva, except those of two types: When there is any suspicion of malignant change, vulvectomy is the only procedure to be considered, and when the patient is so fat that identification of the various nerves would be tedious and perhaps uncertain, vulvectomy provides the quickest solution of the problem.

SUMMARY

The anatomy of the sensory nerves of the perineum is described.

The operation of neurectomy of the sensory nerves of the perineum is described.

Fourteen cases are considered in which this operation has been performed for irritative lesions of the vulva.

The number of cases and the length of time they have been observed do not permit an opinion as to the permanence of the relief afforded by the operation. Nevertheless, it is recommended as the primary treatment in such cases, unless there is any suspicion of malignant change, or the patient is so obese that neurectomy would be difficult and uncertain.

ACUTE ABDOMINAL SYMPTOMS IN ARACHNIDISM

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Several cases of arachnidism, a clinical syndrome due to the bite of the "black widow" spider, the Latrodectus mactans, seen recently at the University of Virginia Hospital presented abdominal symptoms of great severity. If the true condition had not been recognized, exploration of the abdomen for an acute surgical abdominal emergency might have been readily undertaken. The ease with which this confusion might occur—witness the reports of several such patients subjected to operation elsewhere—and the apparent lack of consideration given the subject in the surgical literature suggested this résumé of arachnidism with particular reference to its abdominal manifestations.

The first case af arachnidism that came to my attention, case 1 of the series reported herewith, was not seen until the symptoms had commenced to subside, and the diagnosis was not made until several weeks after the patient had been discharged from the hospital. The diagnosis was made at that time through a conversation with a surgeon [1] in a neighboring city. He described the case of a man who had been sent to him a short time previously for operative treatment of a suspected perforation in a peptic ulcer. He felt that the symptoms and signs were not entirely typical and asked a medical consultant to see the case with him. The internist suspected arachnidism and elicited the fact that the patient had been bitten by a spider a few hours previously. Had this diagnosis not been made, the patient would have been subjected to an exploratory laparotomy for the suspected perforation of a peptic ulcer.

After hearing the symptoms and signs of this case described, I reviewed the history of case 1 and found them to be almost identical. With this background, it was not unduly difficult to make the correct diagnosis in the subsequent cases of the series reported herewith. In fact, case 2 created so much interest that the intern staff made the diagnoses in the later cases and admitted the last two patients, not to the surgical wards as candidates for operation, but to the medical wards for teaching purposes.

REPORT OF CASES

CASE 1.—C. L. S., a white man, aged 29, was admitted to a private room in the University of Virginia Hospital at 7 p. m. on Oct. 10, 1930. He complained of

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1. Bigger, I. A.: Personal communication.

rather severe pain in the abdomen He had awakened at 5 a. m. with a slight tingling pain in the left popliteal space. He had not noticed any swelling or redness at the site. The pain had gradually radiated up the left leg to the scrotum and the left groin. In a short time he had been seized with excruciatingly severe, cramplike pain throughout the abdomen and toward the region of the left kidney. He had consulted his family physician, who had suspected renal colic and had administered morphine by hypodermic injection. He had been slightly relieved, but the cramplike pains had persisted, with exacerbations at intervals of three or four minutes, throughout the day. Because of the persistence of the pain, the patient had consulted another physician, who sent him to the hospital and asked me to see him in consultation

At that time a careful review of the history revealed nothing additional of positive value. There was no knowledge of any recent blow, injury or insect bite. There had been no urinary symptoms, no nausea or vomiting, and the bowels had moved normally that morning.

Examination revealed a well nourished young man in obvious pain, restless and somewhat anxious looking. His temperature was 99.6 F. by mouth; the pulse rate was 52 per minute, and his respiratory rate, 36 per minute. His respirations were rather shallow and somewhat labored. The blood pressure was elevated. There was no evidence of redness, swelling or heat and no pain or tenderness in the popliteal space, the left thigh, the groin or the scrotum. The abdomen was slightly tender throughout, and there was marked rigidity of the abdominal muscles, which felt boardlike. There was a little tenderness in the region of the left kidney. There seemed to be no abnormality of the muscle or tendon reflexes. Repeated urinalyses failed to demonstrate white or red blood cells, and there was no sugar or albumin in the urine. The leukocytes numbered 14,000 per cubic millimeter of blood.

No definite diagnosis was made. The perforation of a peptic ulcer was considered, but there was something indefinable about the consistency of the abdomen, which taken in conjunction with the absence of nausea and vomiting, the slow pulse rate, and the peculiar onset of the symptoms did not seem consistent with this diagnosis. Because of the pain in the left leg and the region of the left kidney, the tentative diagnosis of renal colic was made and continued careful observation advised.

The next morning the patient's pain had subsided to a considerable degree, and the tenderness and rigidity of his abdomen were scarcely perceptible. His temperature was normal, and the leukocytes numbered 12,500. Later that day he felt well enough to go home, and was allowed to do so.

For a few days he was followed by the medical consultant as an office patient, and repeated urinalyses still failed to reveal any abnormal findings. Five days later a small, slightly indurated area was palpable in the left popliteal space. It soon disappeared, however. The patient's history was filed under "no diagnosis." As previously mentioned, the diagnosis of arachnidism was not realized and made until several weeks later, after hearing the history of a case from a surgeon of another city.

CASE 2.—T. D., a white man, aged 21, was admitted to the surgical ward service of the University of Virginia Hospital on Sept. 20, 1931, at 3:30 p. m. He complained of severe pain in the abdomen. He had arisen that morning feeling perfectly well, had eaten fried ham, bread and coffee for breakfast at about 9 a. m., and then had gone to an outhouse toilet and had a normal bowel movement. While there he had not been conscious of anything like the bite or sting of an insect. Half an hour later he had started out of his house but had been seized

suddenly with such a severe pain in the lower part of his abdomen on the right side and extending to the right groin that he had gone back into the house to lie down. The pain had increased so much that he had called his family physician, who administered morphine hypodermically. The pain had persisted, and the physician had sent the patient to the hospital because he suspected some acute intra-abdominal disease that necessitated surgical treatment. There had been nausea but no vomiting. There had been no urinary symptoms or chills.

Immediately after the patient entered the hospital, examination revealed a well nourished, healthy looking young man apparently suffering considerable pain. His temperature was 99 F. by mouth; his pulse good and its rate 104 per minute, and his respirations were 24 per minute. Physical examination gave essentially negative results, except for the abdomen, which was slightly tender throughout and quite rigid. The rigidity was boardlike in character throughout, though a little more marked on the right side than the left. All muscle and tendon reflexes were normal. The leukocytes numbered 10,200, and examination of the urine revealed no abnormality. Four hours later the patient's temperature was 100 F. by mouth, and the leukocytes numbered 13,500. The pulse was of good quality, and its rate was only 70 per minute. In spite of the failure to elicit the history of a spider bite, I made the diagnosis of arachnidism and advised symptomatic treatment rather than the exploratory laparotomy which had been previously considered.

The patient's subsequent course proved the wisdom of this decision, for his symptoms gradually subsided and the next day he was sufficiently well and comfortable to go home. At that time his leukocytes and temperature were normal. Some days later his local physician reported that the man was entirely well and apparently none the worse for his experience.

CASE 3.—N. E. D., a white man, aged 55, the father of T. D. (case 2), was admitted to the surgical ward service of the University of Virginia Hospital on Sept. 29, 1931, at 9 : 00 p. m. He complained of pain in his abdomen, legs and back of about twelve hours' duration. At 7 : 00 a. m. he had gone to the same outhouse toilet as that visited a week previously by T. D. (case 2), and while there felt a sharp, needle-like sting on the right side of his scrotum. He had not seen what stung him and had not given the incident any further consideration. About two hours later, however, he had felt pains in both knees which had radiated up the thighs and localized in the abdomen and back. The abdominal pain had been quite severe and accompanied by nausea and vomiting. He had been most comfortable when lying down with the thighs flexed on his abdomen. During the day the pain had increased in severity, and he had called a physician to see him. The physician, who was not the same one who had attended his son, sent him to the hospital for surgical consideration.

Examination revealed a well nourished, elderly-looking man apparently suffering considerably. His temperature was 101 F. by mouth, the pulse rate 80 and the respiratory rate 24 per minute. His systolic blood pressure was 140 and the diastolic 75 mm. of mercury. The only abnormal physical findings were a small erythematous spot about 1 cm. in diameter on the right side of the scrotum and slight tenderness throughout the abdomen with very marked rigidity of the abdominal muscles. His leukocytes numbered 16,200, but urinalysis revealed no abnormal findings. The intern house officer who admitted the patient to the hospital made the diagnosis of "arachnidism."

The patient improved rapidly, though he suffered from a rather severe and persistent headache. All his symptoms disappeared so that he was able to go home thirty-six hours after the time of his admission to the hospital.

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CASE 4.—W. H., a Negro, aged 31, was admitted to the surgical ward service of the University of Virginia Hospital on Oct. 12, 1931. He complained of severe pain in his abdomen of about twelve hours' duration. His symptoms, signs and physical and laboratory findings did not differ in any essential respect from those recounted in the first three cases, except that he had seen and felt a spider bite him. During the night he had visited an outhouse toilet, and just taken his seat when he felt a sharp sting on the foreskin of the right side of the penis. He had a flashlight with him, and when he illuminated the painful area he saw "a black spider with long legs and red spots on his body" clinging to the skin. The abdominal pain had commenced an hour or two after the spider bite had occurred.

CASE 5.—E. B., a white youth, aged 18, was admitted to the medical ward service of the University of Virginia Hospital on Nov. 18, 1931. He complained of severe abdominal pain of seven hours' duration. He had been awakened at 5 a. m. by the pain and had no knowledge of a previous insect bite. All the features of this case were practically identical with those of the previous four cases so they will not be detailed further.

CASE 6.—J. L. G., a white man, aged 35, was admitted to the medical ward service of the University of Virginia Hospital on Nov. 25, 1931. He complained of extremely severe cramplike pain in the abdomen of ten hours' duration. About an hour before the onset of the pain he had felt a sting of some sort on the right wrist while loading rocks on a wagon from a rock pile. The symptoms and abnormal findings characteristic of the previous five cases were found in this instance too, so that the details will not be repeated.

COMMENT

The most striking feature of all the cases was the relative ease with which the correct diagnosis could be made, even without the history of the bite of a spider, if the condition were borne in mind, but likewise the ease with which the mistaken diagnosis of an acute surgical intra-abdominal disease such as perforated peptic ulcer might be made if one were not familiar with the symptoms and signs of arachnidism.

The outstanding symptom in each case was the severe and usually cramplike abdominal pain, while the most prominent physical abnormality was the extreme boardlike rigidity of the abdominal musculature. Regarding the pain in the abdomen, it is important to note that in most of the cases there was an associated pain or ache in the muscles of the thighs or the back. Concerning the rigidity of the abdominal muscles, it is important to note that the tenderness was much less marked than that usually accompanying the rigid abdomen of a perforated peptic ulcer or appendix.

Arachnidism is characterized by the acute onset of severe pain within from a few minutes to an hour or more after the bite of a spider has occurred. Not infrequently the patient is not conscious of having been bitten at all. The characteristic progress of the pain from the site of the bite to the abdomen is often overshadowed by the severity of the abdominal pain and ignored or forgotten by the patient. The pain may actually commence in the abdomen and remain localized there, though in such a

case it usually does radiate to the back or down the thighs, especially during the subsidence of the most acute symptoms. Nausea and vomiting frequently occur. There is characteristically an elevation of the patient's temperature to from 99 to 101 F. with an accompanying leukocytosis of from 12,000 to 20,000. The patient's pulse rate is usually elevated slightly, but in two of the cases of this series it was lower than normal. The blood pressure is usually elevated. Apparently, rigidity of the abdominal muscles, usually boardlike in character, is present in all cases. Palpation, however, reveals less tenderness than would be expected to accompany the rigidity. Morphine administered by hypodermic injection will relieve the pain partially though not entirely, but the rigidity of the abdominal muscles will not disappear after its use.

This summary of the syndrome shows how closely it may simulate an acute abdominal disease necessitating immediate surgical intervention. At a recent meeting of one of the prominent national surgical societies, a paper dealing with acute abdominal disease was read. During the discussion of the paper, a well known surgeon[2] mentioned a group of cases that he said always puzzled him greatly. He described two cases as typical examples. In each of them the symptoms, signs and laboratory findings were similar to those of arachnidism. In each instance the abdomen had been explored but nothing abnormal found except for an apparent spasm of the entire intestinal tract. For lack of a more satisfactory explanation he had ascribed the symptoms and signs to "enterospasm" of unknown origin. In some subsequent cases he had found that the administration of atropine hypodermically would relieve the symptoms. This was learned too late to try it in any of the cases of arachnidism of this report. Dr. Bryan has subsequently told me that he believes arachnidism to be very unlikely as the cause of the acute abdominal symptoms in at least some of his cases of "enterospasm."

While arachnidism has been discussed frequently and many cases have been recorded in the literature, I have found no reference to the syndrome in textbooks or periodicals devoted to surgery. In many of the recorded cases, however, the patient has been subjected to operation under a mistaken diagnosis.

A very comprehensive review of the literature was made by Bogen[3] in 1926. He added fifteen cases to those already reported and made several interesting observations. Apparently the age and sex incidence is unlimited. Some patients came from large cities while others dwelt in the country. Most of the bites occurred in the evening or early morning in the summer or early autumn.

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2. Bryan, W. A.: Personal communication.
3. Bogen, Emil: Arachnidism: Spider Poisoning, Arch. Int. Med. **38**:623 (Nov.) 1926.

Bogen stated that the Latrodectus mactans, frequently called the "black widow," is the chief and perhaps the only really poisonous spider in the United States. It has been found in almost all sections of the United States.

The following description is taken from his article:

Latrodectus Mactans is a shiny, coal black spider, usually brilliantly marked with red or yellow or both. The female, which is always the one responsible

Fig. 1.—Female Latrodectus mactans caught beneath kitchen porch overhanging outside stairs to basement, Charlottesville, Va. (Hindmost left leg is missing.)

for the bites reported, is often a half inch in length when fully grown, and may stretch its slim, glossy, black legs over as much as 2 inches (5 cm.) [fig. 1]. The markings vary greatly, the most constant being a bright red patch shaped somewhat like an hourglass, on the ventral surface of the abdomen [fig. 2]. The globose abdomen, much larger than the cephalothorax, resembles a black shoe button, although it may have one or more red spots along the middle of the back and over the spinnerts, in addition to the ventral patch [fig. 3]. The male is much smaller than the female and is even more conspicuously marked, having four stripes along each side of the abdomen, in addition to the marks of the

Fig. 2.—Female Latrodectus mactans, ventral aspect, showing "hour-glass," scarlet marking. (Outlined in white for clearer depiction.)

Fig. 3.—Female Latrodectus mactans, showing scarlet spot just cephalad to the spinnerts. (Outlined in white for clearer depiction.)

female. The young spiders are much lighter in color, gradually donning the glossy, black coat in a series of moults over about forty days.

The black widow, as it is called from its custom of eating its mate, is usually found alone, as it will engage in mortal combat with any other spider placed near it. It builds a coarse and irregular dark web in dimly lighted places where it may be undisturbed. Occasionally it is found under stones or pieces of wood or in holes in the ground, in old stumps or bushes, more often in the rafters and corners of little used buildings, in the basements and attics of unfrequented houses, and in the dark corners of barns and other outbuildings, and it has been frequently seen in outdoor toilets, where it builds its web across the seat of the toilet.

More than 150 cases of poisonous spider bites have been reported by thirty-three physicians in the United States during the last century. In several instances the patient was operated on by mistake for an acute appendicitis or other acute surgical abdominal disease, while biliary or renal colic, acute pancreatitis, ruptured gastric ulcer and various forms of poisoning were suggested in others.

Bogen, whose bibliography included 462 references, concluded that "arachnidism or spider bite poisoning is a true clinical entity in the field of general medicine." I might add that this clinical entity may be important to consider in the differential diagnosis of acute surgical abdominal disease.

SUMMARY

Six cases of arachnidism, poisoning from the bite of the Latrodectus mactans, or "black widow" spider, were reported. In some instances the spider bite had occurred without the patient's knowledge. The cases were characterized by the acute onset of very severe abdominal pain, usually nausea and vomiting, boardlike rigidity of the abdominal muscles with more or less tenderness and elevation in the patient's temperature and leukocytes. Attention was called to the ease with which the mistaken diagnosis of acute surgical abdominal disease might be made and the patient subjected to an unnecessary exploratory laparotomy. A previous comprehensive review of the literature by Bogen was briefly alluded to, including his statistics of the incidence of the disease and his description of the spider and its habitat. The importance of arachnidism as a clinical entity to be considered in the differential diagnosis of acute surgical abdominal disease was stressed.

LIGATION OF THE SAPHENOUS VEIN

A REPORT ON TWO HUNDRED AMBULATORY OPERATIONS

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PREVIOUS LITERATURE

In a previous communication one of us (Dr. de Takáts [1]) advocated ligation of the saphenous vein for certain types of patients afflicted with varicose veins. The operation was described as an ambulatory procedure to be used in combination with injection treatment. Since that time we have been able to perform this operation on one hundred and fifty more patients, and are now presenting a report on the total of two hundred cases, describing the indications and contraindications, the statistical data of our material, the technic, postoperative course and complications and the results and recurrences.

Celsus,[2] in his books on medicine, described an operation for varicose veins as follows:

The skin over the vein being incised, the edges are taken up by a small hook and the vein is drawn apart on all sides from the body; and it is guarded against lest among these things themselves, it may be injured. And a blunted little hook is placed under, and about the same space being placed between (four fingers), the same is done in the same vein; whither it may tend is known easily, the little hook being extended. When the same has been done in whatever part varices are, the vein being drawn in one place by a little hook, is cut off; afterward in what part the next hook is, it is drawn and pulled out and there again is cut off. And thus on all sides the leg being freed from varices, then the edges of the wounds are closed together and an agglutinating plaster is cast on over.

Obviously, multiple excision of small segments of vein were made, but no mention is made of cautery or ligature to stop bleeding. Interesting notes about the etiology and operative treatment of veins are found in Ambroise Paré's work, published in 1579:

The matter of them is usually melancholy blood, for varices often grow in men of melancholy temper and which usually feed on grosse meats or such as breed

grosse and melancholy humours. Also women with child are commonly troubled with them by reason of the keeping together of their suppressed menstrual evacuation. It is best not to meddle with such as are inveterate; for of such being cured there is to be feared a reflux of the melancholy blood to the noble parts, whence there may be imminent danger of maligne ulcers, a cancer, madnesse or suffocation.

Paré advocated tying the vein below the knee. The last two complications suggest a frequent occurrence of sepsis and pulmonary embolism, although the idea that the varicose blood was dangerous had already been expressed by Hippocrates. The formation of varicose veins was thought to be an effort of nature to sidetrack the deleterious humors that might otherwise cause madness, etc. This opinion was handed on intact until the discovery of circulation.

W. Turner Warwick [3] gave an excellent description of the gradual evolution of the mechanical theory as opposed to the humoral theory of Hippocrates. The mechanical theory of varicose veins was the consequence of Harvey's theory of circulation, and the importance of valves was gradually recognized.

So far as can be ascertained, Home [4] in 1801 practiced ligation of the saphena magna at the level of the knee, with the view of cutting off the column of blood from ulcers. "Within a few hours after the vena saphena has been taken up the symptoms disappear and the patient is led to take notice of the distress it before gave him and to explain the sense of the suddenness of its removal." The operation was condemned because of the frequent occurrence of sepsis. Brodie, cited by Warwick [2] in his lectures on "Surgery and Pathology," appreciated the value of Home's procedure, but he tried other measures of interrupting the continuity of the vein. He tried open division with a compress, whereas Colles devised a vein truss, and Velpeau a pin which passed underneath the vein with the two ends tied together above it.

This was the status of vein ligation when Trendelenburg,[5] in an aseptic era, revived the theory of reflux and established the operation on a rational basis, stating that the vena cava, the iliac vein and the trunk of the femoral vein below Poupart's ligament usually have no valves, and that if the saphenous valves become incompetent a single wide tubular system exists from the heart to the ankle. He also pointed out that the variations of intra-abdominal pressure would be trans-

3. Warwick, W. Turner: The Rational Treatment of Varicose Veins, and Varicocele, London, Faber & Faber, Ltd., 1931.

4. Home, Everard: Ulcers on the Legs, London, W. Buhmer & Company, 1801.

5. Trendelenburg, Friedrich: Ueber die Unterbindung der Vena saphena magna bei Unterschenkelvarizen, Beitr. z. klin. Chir. 7:195, 1891.

mitted to the saphenous system. To protect this system, he advised saphenous ligature about 3 inches (7.6 cm.) above the knee. Later Perthes, from his clinic, emphasized high ligation at the saphenofemoral junction, as in seven of the seventy-eight cases collaterals developed above the ligature.

The end-results of Trendelenburg's operation were not encouraging. There were from 22 to 72 per cent recurrences reported,[1] so that the method, practiced alone, fell gradually into disrepute. In addition, the percentage of fatal embolism following this operation was estimated from a large personal series of Bernsten as 0.7 per cent. This astonishingly high percentage of embolism has kept many surgeons in constant fear of vein ligations. In reading the description of Trendelenburg's operation, we find that following vein ligation, the patient's legs are bandaged from the ankle to the site of ligature, and are splinted and immobilized for three weeks. These procedures, we fear, are not the proper measures to combat embolism, but are important factors in producing it.

On analyzing our results with the injection treatment for varicose veins,[6] we found a definite percentage of recurrences, which were due to recanalization of the obliterated veins because of an uninterrupted reflux from the proximal segments of the saphenous vein. Therefore, ligation of the saphenous vein was introduced as an adjunct to the injection treatment, preventing backflow, serving as a barricade to ascending phlebitis and reducing materially the number of necessary injections.[1] The combination of injection treatment with vein ligation was not new; Tavel,[7] Schiasis [7] and Moszkovicz [8] advised such a procedure. However, no emphasis has been laid on the importance of the ambulatory type of ligation. Aside from the economic aspect of saving the patient hospital expenses and permitting him to continue work after two days, we hope that the danger of embolism may be obviated or reduced to a minimum in the ambulatory patient.

No smaller authority than Theodor Kocher [9] had his patients get up the second day after a high saphenous ligation, which he combined with multiple percutaneous ligatures of Schede; sometimes as many as two hundred ligatures were employed on one patient. Such patients were allowed to get up the second day and were discharged on the

6. de Takáts, Géza, and Quint, Harold: The Injection Treatment of Varicose Veins, Surg., Gynec. & Obst. **50**:545 (March) 1930.

7. Cited by Sicard, J., and Gaugier, L.: Le traitement des varices par la méthode sclérosante, Paris, Masson & Cie, 1927.

8. Moszkovicz, Ludwig: Behandlung der Krampfadern mit Zuckerinjektionen kombiniert mit Venenligatur, Zentralbl. f. Chir. **54**:1732 (July 9) 1927.

9. Kocher, Theodor: Vereinfachung der operativen Behandlung der Varizen, Deutsche Ztschr. f. Chir. **138**:113 (Nov. 1) 1916.

fifth day. In our series not one patient, whether a dispensary or a private patient, has been hospitalized, and in the two hundred patients we have not observed a single embolism or pulmonary infarct.

INDICATIONS AND CONTRAINDICATIONS

The preliminary report has already stated [1] that when the long saphenous vein is visible or palpable above the lower third of the thigh, the ligature is preferred to injections at this level. It is, of course, possible to make injections into the saphenous vein above this point or even just below Poupart's ligament and produce an obliteration of the vein, but there are several reasons why to us an aseptic ligature seems more advisable in such cases. First, injections are sometimes impossible above the middle of the thigh, because the vein dips deeper and deeper in the subcutaneous fat and may not be palpable at all in spite of existing valvular incompetence. In such patients, if injections are made at a lower level, an ascending thrombosis will make the previously unrecognizable vein suddenly manifest and palpable to the saphenofemoral junction. This progressive, ascending thrombus has none of the characteristics of the thrombus produced at the site of local intimal irritation. It is a stagnation thrombus (static thrombus of Aschoff), and is soft, friable and hardly adherent to the wall. Given the other possibility, that the vein is widely patent to its junction with the femoral vein and injections can be made into it, clots of formidable size, which have been seen to attain 5 cm. in width (fig. 1) cannot be regarded as harmless. The frequently expressed idea of McPheeters,[10] that embolism is not to be feared because of the reversed flow of blood in the varicose vein, refers only to the upright position; certainly in the horizontal position the pressure in the veins of the extremities is negative.

An equally important reason for advocating ligature of the saphenous vein at high levels is frequent canalization of thrombi if the back-pressure of blood is permitted to persist. It was with the idea of diminishing the incidence of recurrences that the ambulatory vein ligation was proposed. The backpressure in previous measurements was as high as 210 cm. of water.[11] Our idea has been corroborated and extended by convincing histologic evidence through the significant work of Howard, Jackson and Mahon.[12] They reported the strikingly high

10. McPheeters, H. O.: Varicose Veins, ed. 3, Philadelphia, F. A. Davis Company, 1931, p. 71.

11. de Takáts, Géza; Quint, H.; Tillotson, I. T., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, Arch. Surg. **18**:671 (Feb.) 1929.

12. Howard, M. J.; Jackson, C. R., and Mahon, E. J.: Recurrence of Varicose Veins Following Injection: A Study of the Pathologic Nature of the Recurrence and a Critical Survey of the Injection Method, Arch. Surg. **22**:353 (March) 1931.

incidence of 79 per cent recurrences caused by recanalization. That a totally occluding superficial thrombophlebitis may result in a recanalization of the vein has been seen in five personally observed cases. The double ligature with excision of a segment of at least 3 cm. in length is a permanent block, although a possibility of a "detour" will be discussed later.

In the first communication it has also been stated that the average number of necessary injections following ligation could be reduced from twenty-one to six. The same observation could be made in the present larger series.

Another indication for tying the saphenous vein has been an ascending thrombosis of a spontaneous phlebitis if one is able to ligate above the thrombosis. We have recognized this indication in five cases of acute ascending thrombophlebitis. The ligature not only acts as a barrier to the distal clot, but seems to alleviate the pain by removing the tension of backpressure from the inflamed vessel. These patients have not been strictly ambulatory, as they have been admitted to the hospital and kept in bed for a few days. However, as soon as the fever and pain subsided, they were allowed to get up, and they were home on the fourth day. In addition, other measures were used to hasten absorption of the periphlebitic exudate, the discussion of which is not within the scope of this paper.

The contraindications to ligation of the saphenous vein are few and definite. In the first place, if the venous dilatations are present only below the knee and the long saphenous vein is not palpable even at the level of the inner condyle, the operation is not necessary. Secondly, if there are multiple incompetent anastomoses between the deep and the superficial system, a high ligature of the saphenous vein will not prevent the inflow from the deep veins. In such patients an attempt may be made to make multiple ligations of the incompetent anastomoses. For such multiple ligations we prefer to admit the patient to the hospital for twenty-four hours, just for his comfort, but not with the idea of immobilizing him for any length of time. If there are too many incompetent valves, a high ligation followed by excision and stripping is our method of choice.[6]

Thirdly, the vein ligation is not indicated if a deep venous block is present. Men of great experience in this line, such as McPheeters, have stated that they have never seen a lack of patency in the deep vein. It is, of course, well known that a clot in the deep veins becomes permeable after a certain length of time either by a true canalization of the thrombus or by a reestablishment of circulation through short collaterals and the vasa vasorum. Nevertheless, following a deep venous thrombosis, a certain degree of venous insufficiency persists,

and the ligature of a compensatory dilatation does not seem logical. It may not aggravate the edema, but it will hasten the development of other collaterals. One must also consider the effect of old canalized thrombi on the important femoral valve at the level of Poupart's ligament, which protects the limb from backpressure.

G. P., aged 46, had a left-sided deep thrombophlebitis following childbirth. Twenty-six years later she was seen with a tortuous long saphenous vein, into which a large anterolateral branch emptied. The Trendelenburg test gave a positive result. The Perthes test showed deep patency. There was no edema. A high ligation of the saphenous vein was performed, and multiple injections were made into the thigh and calf distally to the ligation. The patient made an uneventful recovery; at the time of her discharge all the veins were obliterated. There was no edema. One month later, the vein into which injections were made was firmly obliterated, but a new large channel was visible, running parallel with the original vein. The vein started from above Poupart's ligament and was obviously not an overlooked saphenous branch. We have interpreted this recurrence as the result of increased venous pressure in the deep veins, which opened up new superficial veins.

To sum up, then, ligation of the saphenous vein is indicated: (1) in valvular incompetence of the long saphenous vein above the lower third of the thigh, (2) in valvular incompetence of the anastomotic branches, if they resist injection treatment and (3) in ascending thrombophlebitis of the saphenous vein.

The operation is contraindicated: (1) when the vein is not involved above the knee, (2) when there are multiple incompetent valves in the communicating branches which cannot all be ligated and (3) when there is evidence of insufficient deep venous return owing to an old deep phlebitis or a deep valvular insufficiency.

TECHNIC OF AMBULATORY VEIN LIGATION

It would hardly seem necessary to describe a simple vein ligation in detail. Nevertheless, there are a few minor details that are significant because the operation is performed on ambulatory patients. The operations were done in a sterile operating room either at the hospital or in a perfectly equipped operating room of the surgical dispensary, with all necessary precautions such as masks and mouth pieces covering the nose. In the standing position the course of the vein is marked out with a 2 per cent solution of brilliant green. The skin is shaved dry just before the operation and prepared with ether, iodine and alcohol. The line of incision in high saphenous ligations runs about a handwidth distally and parallel to Poupart's ligament and should start mesially to the palpable femoral artery. Naturally, if the vein is palpable at this level, a shorter incision of from 3 to 4 cm. is sufficient. Generally we prefer transverse incisions, because thus some of the accessory saphenous branches are caught and tied. However, if a

longer segment of vein should be excised with its insufficient anastomotic branch, a longitudinal incision is more useful.

The line of incision is infiltrated with 0.5 per cent procaine hydrochloride with 3 drops of 1 : 1,000 epinephrine to each ounce (fig. 1). Only a superficial subcutaneous infiltration is made, and repeated aspirations are made for blood. Because of the vicinity of the large vein, care must be taken not to inject any procaine hydrochloride intravenously. In one patient, as reported in our previous article,[1] only a few drops of procaine hydrochloride were sufficient to produce pallor, tachycardia and numbness of the lips and fingers. The toxic effects wore off in a few minutes, but illustrate the necessity of extreme care in this region to avoid intravenous injection.

Figure 1   Figure 2

Fig. 1.—Ligation of the right internal saphenous vein. A week later a massive clot was palpated above the knee. The left side has not been treated.

Fig. 2.—The course of the vein is outlined in the standing position at the highest palpable point with a 2 per cent aqueous solution of brilliant green. Five-tenths per cent procaine hydrochloride solution with 3 drops of epinephrine, 1 : 1,000, is used to infiltrate a transverse line of incision. Beware of intravenous injection!

After waiting about five minutes for a complete anesthesia, incision is made through the skin and subcutaneous fat. In some patients a strong tortuous anterior branch lies immediately under the skin and needs no further exposure. This, however, may not be the main trunk, but a collateral from the superficial epigastric, overcoming a previous iliac block. At this high level (three fingerbreadths below Poupart's ligament) the main trunk lies below the superficial fascia and has to be exposed at a depth of from 2 to 4 cm., or sometimes even more. When the main vein is exposed, a perivenous injection is made on both sides of the vein as traction on the perivenous sympathetic fibers produces pain (fig. 2). A curved artery forceps

or aneurysm needle armed with no. 1 chromic catgut is insinuated under the vein twice (fig. 3). The two ligations are tied at a distance of 3 cm. or more, and the segment of vein is well lifted up to detect communicating branches from the deep veins, which should also be carefully tied as they may produce a profuse hemorrhage (fig. 4). It is important to place the proximal ligature as close to the femoral junction as possible, leaving a very short stump. As an added precaution a second ligature may be applied to the proximal stump, as considerable pressure is exerted on it in the ambulatory patient.

The segment of vein is then removed, and it is used for bacteriologic study. Before the wound is closed the patient is asked to cough a few times to catch, if

Fig. 3.—A short transverse incision is made through the skin, the subcutaneous fat and, if necessary, the superficial fascia. When the vein is exposed, a few drops of procaine hydrochloride are injected around it.

Fig. 4.—A curved artery forceps, carrying a number 1 chromic catgut ligature, is passed under the vein. The vein is lifted up, and another ligature is placed at least 1 inch proximal to the first one. The proximal ligature should be close to the saphenofemoral junction.

necessary, additional bleeders. No sutures are placed in the subcutaneous fat, and the skin is closed with interrupted dermal sutures. The skin around the incision is now painted with a mastic solution,[13] and the gauze is stuck to the skin with the solution (fig. 5). In ambulatory patients who perspire freely, sweat and dirt cannot be kept away from the incision with the usual adhesive tape bandage. This solution, which one of us has used exclusively since 1914 in all aseptic operations, keeps the skin around the incision dry and protected. We strongly emphasize its

13. Gum mastic, 40 Gm., benzene, 60 cc., castor oil, 20 drops; then add sufficient M. Sc. **184**:57 (July) 1932.

use here, particularly in dispensary patients, who sometimes return with soiled and slipped dressings.

The patients return for inspection in forty-eight hours, and the stitches are removed on the eighth day. They are asked to stay away from work for the first two days and may return to work after the first inspection. They should not stay in bed during the day for any time.

Fig. 5.—Both ligatures are tied. The segment of vein between the two ligatures is excised. No clamps are used at any time.

Fig. 6.—The bleeding is accurately controlled. Interrupted dermal sutures approximate the edges of the skin. The skin around the line of suture is painted with a solution of mastic in benzene, and a layer of gauze is stuck to the skin, which produces a water-tight dressing. Elastic compression is applied on top.

ANALYSIS OF MATERIAL

Age, Sex and Previous Treatment.—This report is based on two hundred ambulatory vein ligations, performed on dispensary patients [14]

14. The operations were performed by Drs. Zimmermann, Jacques, Quillin and Quint, members of the Varicose Vein Clinic.

and in the private practice of the authors. The patients' ages, classified in decades, were as follows:

Decades	Number of Patients
10–20	2
20–30	30
30–40	69
40–50	58
50–60	34
60–70	5
70–80	2
	200

Ninety-five per cent of the patients were between 20 and 60 years of age, 1 per cent between 10 and 20 and 1 per cent between 70 and 80.

There were ninety-four female and one hundred and six male patients, illustrating, as has been pointed out before, that at least in our material there is no feminine prevalence.

As to occupation, all walks of life are represented, the majority of cases occurring in patients giving a history of long hours on their feet or hard manual labor in the upright position.

The influence of heredity, studied in a previous report,[6] was again very striking. Particularly significant seems the observation that whenever varicose veins are encountered in the young both parents were affected.

The previous treatment of these patients was as follows:

140	Had had no previous treatment
3	Had had surgical excisions (but no high ligation)
8	Had worn Unna's casts
49	Had had injection treatment

200

Of the three surgical excisions, not one could be called radical, judging from the scars. The saphenous vein was not ligated below Poupart's ligament, and short scars were present on the calf and thigh. In the eight cases in which Unna's casts had been applied for varicose ulcers elsewhere, the patients were not progressing rapidly and there was a marked reflux of blood from above. Of greatest interest are the patients who had had injection treatment elsewhere or from us. It is this group that made us realize that the number of recurrences, reported elsewhere as 10 per cent, should be reduced by ligation. These patients fall into two groups: one in which obliteration was never accomplished (in one case as high as fifty injections were given) and another in which early recanalization took place. In the private practice of one of us, ligations in patients who had previously been given

injections became necessary seven times because of repeated recurrences. Since the ligations, recanalization has not occurred in this group.

The postoperative disability was estimated as follows (all patients were told to take one day off following the operation):

Number of Patients	Disability
161	None
22	1 day
8	2 days
3	3 days
3	4 days
1	8 days
1	9 days
199	

An analysis of patients who were disabled for more than two days will be made in the section on complications.

Complications.—One patient had a hemorrhage owing to the slipping of the proximal ligature. She was taken to a hospital, where the hemorrhage was controlled. The patient made an uneventful recovery. In one patient a hematoma developed, which produced a serous discharge for nine days and then healed up completely. In one patient a wound infection developed on the fourth day; the abscess was opened. The patient was not hospitalized, and the wound healed in eleven days.

One patient died of streptococcic septicemia. A wound infection developed in this patient, which was obvious on the fourth day, but for various reasons the patient could be hospitalized only on the tenth day, when he was admitted with a generalized streptococcic septicemia. Death occurred as a result of the infection. At autopsy no thrombosis of the proximal saphenous stump or of the femoral vein was found. Death occurred because of a surgical infection, which was localized but because of improper after-care resulted in a generalized infection.

One patient, whose case was reported in our previous series, had a slight procaine hydrochloride reaction during the operation owing to an intravenous injection of the drug. The toxic symptoms disappeared within a few minutes.

A tabulation of complications shows the following:

Procaine hydrochloride reaction	1
Hematoma	1
Postoperative hemorrhage	1
Wound infection	1
Death from septicemia	1

We believe that all of these complications are preventable, at least to a minimum. They have not occurred in our private work. The

procaine hydrochloride reactions will not be encountered if frequent, careful aspirations are made for blood before the drug is injected. Hematomas can be reduced to a minimum if all tributaries are carefully tied, if the patient is asked to cough or strain before closing the wound and if a tight pressure bandage is applied. Slipping of the proximal ligature occurred once; since that time, a double ligature has been placed on the proximal stump. Care must be exercised to leave a large enough segment of the vein distal to the ligature. The one death from septicemia was due to an initial surgical infection, which unfortunately still occurs in any large group of aseptic operations. It is probably unavoidable at the present time, although all operations were carried out under strict aseptic precautions, with masked head, nose and · mouth. The measures that should be carried out, however, in all cases showing infection consist in immediate hospitalization, immobilization and hot wet dressings, with incisions when necessary.

Secondary infection from the skin in these ambulatory patients is also a possibility. We strongly emphasize the use of the glue, the mastic solution, which forms a watertight contact between the skin and dressing and prevents perspiration.

Thrombosis Following Vein Ligation.—Of the two hundred patients, sixty-five, an incidence of 32.5 per cent, showed a massive thrombosis distal to the ligature. Of this group, forty, that is, 20 per cent of the original two hundred, showed complete obliteration, which did not necessitate further injections. It seems obvious that it is in this group of patients who are cured after Trendelenburg's vein ligation, although none of the older statistics bring out this point, that the patients who have a distal thrombosis following the operation are the ones who remain cured. It is because of the comparatively frequent occurrence of distal thrombosis that we do not advocate injections at the time of ligation, as they may not be necessary or they may even activate a resting infection.[15]

The thrombosis following ligation may be purely static and aseptic, occurring in the form of a narrow, firm cord, with no inflammatory reaction around it, but more frequently it is accompanied by a massive periphlebitic exudate, which is hot and tender on pressure but does not lead to an elevation of temperature. Of the eight patients who were disabled more than two days, five belonged to this group. If the patients are given proper elastic support in the form of Unna's paste boot or an elastic adhesive bandage, they are comfortable. They should not be put to bed, but should be encouraged to be up and around, as we think that the ambulatory ligation is our real safeguard against embolism.

15. de Takáts, Géza: The "Resting Infection" in Varicose Veins, Am. J. M. Sc. **184**:57 (July) 1932.

The thrombosis in the proximal stump is, of course, of even greater interest and has been carefully looked for in every case. The idea of some surgeons, that every vein ligation results in a massive clot proximal to the ligature, cannot be substantiated. If the vein is occluded with a ligature without first crushing it with artery forceps, the endothelial damage is small and nothing but a microscopic clot results. The classic experiment of Baumgarten, who showed that blood did not have to clot in the vein between two ligatures, should be recalled. If one could not tie a vein without the danger of embolism, surgeons would have to cease to operate entirely.

Of the two hundred vein ligations, there was a palpable clot in the proximal stump in eighteen (9 per cent). Occasionally a large varix at the level of Poupart's ligament, obviously above the saphenofemoral junction, would diminish in size or disappear. We have become more and more impressed with the facts, which have already been stressed by Margrit Hanselmann [16] in an inaugural dissertation, that the longer the proximal stump, the more apt is the proximal clot to appear, and that ligation close to the saphenofemoral junction is the best measure to avoid large clots in the proximal stump. Thus, aside from the ambulatory operations, the shortness of the stump is another safeguard against massive embolism.

Of the eighteen patients showing a proximal thrombosis, all but three had a distal thrombosis, which is suggestive of an increased endothelial reactivity of the patients. According to Dietrich, one of the foremost pathologists, the increased susceptibility of the endothelial lining is an important factor in thrombus formation.[17]

Whether it is possible to predict the occurrence of a distal or proximal thrombosis following vein ligation is an open question. Elsewhere one of us described simple methods of detecting resting infection previous to injection treatment.[15] The same procedures, namely, provocative vein puncture, diathermy or roentgen exposure, can be used to diagnose a latent infection or an increased susceptibility of the vein. However, such "flare ups" are much less frequent following ligation than after injections, because a ligature is much less irritating to the vein than an injection.

The occurrence of a proximal clot in 9 per cent of our cases makes one wonder why injections at high points would not be equally satisfactory so long as the ligature also produces a fairly large clot. We

16. Hanselmann, Margrit: Postoperative Thrombose und Embolie und ihre Prophylaxe, Inaug. Diss., Zurich, 1926.

17. Dietrich, A., and Schröder, K.: Abstimmung des Gefässendothels als Grundlage der Thrombenbildung, Virchows Arch. f. path. Anat. **274**:425, 1930.

have stated our standpoint in discussing the indications for ligation. The small aseptic clot, the permanent interruption of the venous channel with no chance of recanalization and the possibility of going up within an inch or less of the saphenofemoral junction and catching all branches not only make the operation safer, but also give a better prognosis so far as the end-results are concerned. The statement that the irritative thrombus is safer than the aseptic ligature thrombus because the former is more firmly attached holds only in cases in which the irritative thrombus is aseptic. Since, however, we have shown in our clinic that of fifty-eight clinically uninfected veins more than half gave a positive bacteriologic culture, we hesitate with injections for fear of a progressive thrombosis with inflammatory reaction. That the ligature can be safely applied under such conditions is best shown in patients whose veins have been tied during an acute ascending phlebitis with no reaction in either stump. The course of the five patients whose saphenous veins were tied during an acute attack of ascending superficial phlebitis was so satisfactory that such a procedure must always be considered, without prolonged immobilization.

Results of Vein Ligation.—In the present material a distinction must be made between the dispensary material (one hundred and thirty-five cases) and our private material. Both groups serve to elucidate important points.

The dispensary material contains eighteen patients who had previously been given injections elsewhere or by clinicians in our group, with no results. In these cases a total of two hundred and one treatments have been given with no obliteration, whereas following ligation the patients were discharged as cured after a total of fifty-seven treatments. The cases show such a striking effect of this operation on the right type of patients that we have tabulated the results individually (see the accompanying table). Patients 8 and 13 had partial excisions with stripping of the vein, but no high saphenous ligation. The veins were obliterated in six cases, eight injections being given following ligation. Patient 16 was treated with "many injections" elsewhere, so that the number of treatments is not included in the treatments preceding ligation.

We had originally hoped to present exact follow-up statistics of the entire material of two hundred cases. This was only possible of approximately one third of the dispensary material, although a real effort has been made by our social service department to have the patients appear for reexamination. In the private work of one of us it has been possible to secure exact data in 91 per cent of the cases in which operations were performed. The patients came in every three months for the first year, every six months the second year and

then once a year for the next three years. The first ambulatory vein
ligation was performed in 1927; the first patient was under observation
for four years.

As the dispensary material could not be adequately controlled for
follow-up purposes, we shall limit ourselves to a discussion of the private
cases, of which sixty exact records are available.

Of the sixty patients, in five a dilatation developed above the ligature.
Four of these patients were operated on in 1927 or 1928, when ligatures
were placed at the midthigh. Since then we have learned to insist on
a high ligation at the saphenofemoral junction. One patient who had
had a bilateral high ligation returned with a large dilatation at Poupart's
ligament just above the scar, but only on the right side. The only

Results of Vein Ligation Following Unsuccessful Injections

Patient	Number of Unsuccessful Treatments	Number of Treatments After Ligation	Follow-Up Notes*
1	20	6	Complete obliteration
2	2	1	Complete obliteration
3	2	5	No recurrence in 6 months
4	10	0	Total thrombosis
5	5	3	Excellent results; seen after a year
6	6	2	Complete obliteration
7	14	1	Excellent result
8	Vein stripping	0	Complete collapse
9	11	6	No record
10	24	1	Complete obliteration
11	23	4	No recurrence in 4 months
12	2	4	Complete obliteration; ulcers healed
13	Vein stripped	9	Complete obliteration
14	7	2	
15	50	0	Complete thrombosis
16	"Many injections"	6	Complete obliteration
17	20	0	Complete obliteration
18	5	7	Complete obliteration
	201	57	

* The notes were made at least three months after operation. The patients were asked to
return every three months for a year.

possible explanation was that this patient's femoral valve was deficient
or absent, which fact was corroborated by the unusually strong impulse
in this vein following coughing or straining. At reoperation a large,
thin-walled, saccular dilatation was found between the proximal ligature
and the saphenofemoral junction. This was completely excised, the
new ligature being placed at the saphenofemoral junction. The exposed
femoral vein showed such marked fluctuations to inspiration, coughing
or sneezing that the diagnosis of the absence or incompetence of the
femoral valve was certain. The significance of this anomaly must be
investigated in other cases.

Recurrences caused by a marked reflux through incompetent per-
forating veins occurred only in two of the sixty patients (3 per cent).
We have previously stated [6] that patients with large incompetent com-
munications between the deep and superficial veins must have a radical

excision. Quite recently we have tried to ligate the incompetent perforating branches at the time the high saphenous ligation was done, but we cannot report any end-results at this time.

A summary of the recurrences following vein ligation combined with injections in sixty private cases is as follows:

Dilatations proximal to the ligature (4 low ligations, 1 incompetent femoral valve) 5
Dilatations distal to the ligation (incompetent perforating veins)..... 2
_____
7

The final analysis of these recurrences [18] indicates that high ligations should be done in every case, and that either the incompetent perforating veins should be ligated or a radical excision should be made. When one considers, furthermore, that patients who are submitted to vein ligation suffer from the most extensive and progressive type of varicose veins, the end-results show that the combination of vein ligation with injections offers in the suitable type of patient the best chances for permanent results.

Embolism Following Vein Ligation.—In the two hundred cases of ambulatory vein ligation we have not encountered any case of pulmonary embolism or ascending deep thrombosis. One cannot state that the operation is entirely free from this risk, because no operation is. We do believe, however, that two factors, namely, the ambulatory management and the shortness of the proximal stump, are important in the prevention of embolism. The classic description of ligation of the saphenous vein, which called for splinting and three weeks' immobilization in bed, showed the alarming percentage of 0.7 per cent of fatal pulmonary embolisms. When statistics will be available of at least one thousand ambulatory vein ligations, some statement may be made as to the frequency of this complication. We have good reason to believe, though, that they will compare favorably with minor ambulatory operations in this respect.

CONCLUSIONS

On the basis of two hundred ambulatory vein ligations combined with the injection treatment for varicose veins, we think that this procedure has a definite place in the treatment for this condition. The high saphenous ligation protects the treated veins from fluctuations

18. These recurrences indicate that when ligation of the saphenous vein combined with injections was done with proper indications and proper technic a recurrence was found in one of sixty cases (0.6 per cent). This one recurrence was due to an incompetent femoral valve, a condition that we have overlooked entirely up to the present time.

of abdominal pressure and hydrostatic pressure, thus preventing canalization of the thrombi. It also reduces the necessary number of injections and places the occluding ligature close to the saphenofemoral junction. By insisting on a short proximal stump and on ambulatory management, we can report no embolism in the entire series. The complications reported in this series all seem avoidable with growing experience. The end-results of the operation combined with injections show a far smaller percentage of recurrences than those obtained with any other procedure in the treatment for varicose veins.

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AVERTIN AS AN ANESTHETIC FOR GENERAL SURGERY

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In order to determine the worth as well as the limitations and dangers of the various new anesthetic agents, it is desirable that reports of many cases from different clinics be made. With this in view I have undertaken a critical analysis of the cases in which avertin was used either as the anesthetic or for basal narcosis supplemented with some form of inhalation anesthesia in the surgical clinic of the University of Michigan Hospital. This statistical survey covers the period from November, 1929 (when avertin was first adopted in this clinic), to January, 1932, and comprises 430 cases. Operations done in the divisions of genito-urinary and orthopedic surgery in which avertin was employed are included, but the cases in the neurosurgical field have been reserved for a separate report. While avertin was not used as a routine measure for any particular type of work, it was employed rather extensively in abdominal operations and also in operations performed on the face or about the mouth. In all of these cases considerable discretion was exercised in the selection of the patients. Ordinarily cachectic or very elderly persons as well as those greatly debilitated from chronic disease were excluded. In such patients the risk of pulmonary complications arising from a prolonged postoperative period of somnolence seemed to be unwarranted, and for them another anesthetic was usually selected.

AGE AND SEX

The age according to decades and the sex incidence of the 430 cases are shown in table 1. The preponderance of men over women is of no significance as it simply reflects the fact that in this clinic there are more male than female surgical patients. While avertin was used fairly often for children, the instance of the patient 83 years old was an exceptional one. The average age of 36.2 years is an interesting figure, since it shows that fairly young and reasonably sound patients made up the majority of the group.

DOSAGE

The dose in milligrams was in all instances calculated according to body weight. Table 2 shows the doses expressed in milligrams per kilogram which were employed. It will be noted that 110 mg. per kilogram was almost our standard dose. This was occasionally increased in some exceptional circumstances, and likewise on some occasions it was reduced. A dose of 110 mg. per kilogram has seemed to be satisfactory and safe, whereas at no time has it been my aim through either

TABLE 1.—*Age and Sex Incidence*

Age by Decades	
1–9	9
10–19	69
20–29	77
30–39	107
40–49	69
50–59	59
60–69	82
70–79	6
80–89	2
Total	430
Youngest patient	4
Oldest patient	83
Average age	36.2 years
Sex	
Males	232=53.9%
Females	198=46.1%

TABLE 2.—*Dose of Avertin*

Mg. per Kg.	Number Cases	Per Cent
130	9	2.08
125	3	0.78
120	24	5.47
115	12	2.86
110	344	79.96
100	25	5.73
90	4	1.04
80	8	1.82
50	1	0.26
Total	430	100

the use of excessive doses of avertin or the use of heavy preoperative medication to produce complete surgical anesthesia without some form of reinforcement. The addition of a supplemental anesthetic such as nitrous oxide and oxygen or ether is without question a safer method. While 110 mg. per kilogram is a somewhat larger dose than that used by many surgeons, it has not seemed objectionable in my hands. When the smaller doses were employed, the results were considerably less satisfactory. With regard to children, my experience has been in accord with that of others, i. e., that they are more tolerant to avertin than adults, and even with doses of 110 mg. per kilogram, supplementary anesthesia was required in every case.

ADMINISTRATION

Almost as a routine procedure the patients were narcotized in their own beds in the ward or private room. The general standard technic of administration recommended by the makers of the drug was followed. Cleansing enemas were given in the evening before the day of operation but ordinarily not on the operative day. Occasionally a mild sedative was given on that same evening. Most of the patients received some form of preoperative medication. This consisted for the most part of morphine sulphate, from ⅙ to ¼ grain (11 to 16 mg.), or a mixture of opium alkaloids hydrochlorides, ⅓ grain (22 mg.). Atropine was usually omitted, while rarely hyosine, from ⅟₁₅₀ to ⅟₁₀₀ grain (0.4 to 0.6 mg.), was used in conjunction with morphine. The calculated quantity, ranging approximately from 175 to 300 cc. of the 3 per cent solution of avertin which had previously been prepared by an expert pharmacist and kept at a temperature of 40 C., was administered by a nurse anesthetist. The fluid was introduced into the rectum through an ordinary male catheter with funnel attached and was allowed to flow in slowly by force of gravity. The ease of the induction and the absence of an excitement stage or struggling were noteworthy. The induced sleep seemed to resemble natural sleep more closely that that brought about by any other artificial means. The color of the patient was usually good, and there was an absence of marked sweating. Cyanosis was rarely noted. In from fifteen to thirty minutes the full depth of the narcosis was reached, and at or slightly before this time the patient was transported to the operating room. The transfer to the operating table, the preparation of the skin and the arrangement of drapings were carried out as usual. If cutaneous stimuli provoked a reflex response, a supplemental inhalation anesthetic was started at once. Otherwise, the operation was started and reinforcement resorted to when and if it became necessary.

TYPES OF OPERATION

The various operations that were performed are shown conveniently grouped in table 3. It will be noted that considerable use was made of avertin in operations about the head or in the mouth as well as in the various abdominal operations. In the former type of operation, where gas masks or ether cones are apt to encroach on the operative field and so hamper the operator, an anesthetic substance that can be introduced into the circulation by way of the rectum has outstanding advantages. In the laparotomy group avertin gave important assistance in bringing about the requisite degree of muscular relaxation. The second column of figures in the table is of interest. It designates the number of cases in which no supplemental anesthetic was required and shows that this was chiefly in operations which did not involve opening the peritoneal cavity. It is of some interest that only 5, i. e., 12.5 per cent. of the

goiter operations (which ordinarily can be done under comparatively light anesthesia) were completed with avertin unassisted. This seems to bear out the observation that hyperthyroidism produces a greater tolerance to avertin, while conversely hypothyroidism is said to render a patient less tolerant and in such cases the dose should be correspondingly reduced. In keeping with this it was also frequently found that in using nitrous oxide and oxygen with avertin the ratio of the gases had to be kept at approximately the same level as in the cases in which no avertin was used.

TABLE 3.—*Operations under Avertin*

Type of Operation	Total Number	Number Performed with Avertin Unassisted
Face and mouth...................................	68	40
Hernia (all varieties).....	54	11
Kidney and ureter.............	47	10
Gallbladder and biliary tract....	44	7
Thyroidectomy.................	40	5
Appendectomy.................	36	14
Plastic.....................	21	5
Exploratory laparotomy......	20	4
Bone and joint..........	19	5
Resection cervical glands.....	18	6
Breast.....................	10	4
Miscellaneous................	9	5
Gastric resection..........	9	4
Gastro-enterostomy..........	7	0
Lumbar sympathectomy...	6	1
Bladder and urethra...........	5	0
Colostomy......................................	4	2
Amputation (thigh or leg)...	3	1
Cholecystogastrostomy........	2	2
Esophageal diverticulectomy...	1	1
Duodenum...	2	1
Pericardiotomy..	1	1
Gastrostomy...................	1	1
Splenectomy................	1	0
Lobectomy (pulmonary).....	1	0
Gastrocolic fistula..........	1	0
	430	130

SUPPLEMENTARY ANESTHESIA

Table 4 indicates the number of the cases in which supplemental inhalation anesthesia was necessary. As will be noted, nitrous oxide and oxygen was the supplemental anesthetic of choice and was used in the great majority of cases. In 33 cases this alone was not sufficient, and a moderate quantity of ether vapor was given through the McKesson machine. The 21 cases in which ether alone was used for reinforcement call for some comment. These cases were of two types: The first group involved operations done inside of the mouth where anesthetic apparatus was objectionable. In these cases the avertin was supplemented at intervals with ether given through the ether vapor apparatus. The other group was composed of very major abdominal

procedures in which most complete muscular relaxation was necessary, such as lumbar sympathectomy and operations on the biliary tract or deep in the pelvis in muscular persons. A synergistic effect between avertin and ether was noted, and in many cases the ether was necessary only during the preliminary exploration of the abdominal cavity and the packing off process, and could be discontinued during the remainder of the operation with possibly a small quantity again for closure of the peritoneum. Thus the total quantity of ether would range from only ½ to 2 ounces in many of the cases, with nevertheless a high degree of muscular relaxation. When nitrous oxide with oxygen was the supple-

TABLE 4.—*Supplementary Anesthesia*

	Number Cases	Per Cent
None	120	20.23
Gas	246	57.21
Ether	21	4.83
Gas and ether vapor	33	7.63
	430	100

TABLE 5.—*Evaluation of the Anesthetic*

	Number	Per Cent
Good	235	54.64
Satisfactory	64	14.95
Fair	48	11.08
Excellent	42	9.79
Very good	25	5.93
Poor	16	3.61
	430	100

mental anesthetic, the percentage of oxygen in the mixture could usually be considerably increased. The average ratio of the gases used for this entire group was 82: 18 which, of course, means that the percentage of oxygen is practically double the amount possible when used with nitrous oxide alone. Oftentimes the percentage of the oxygen in the mixture was considerably higher than this, starting with a 90: 10 ratio of the gases and tapering off to perhaps a 50: 50 ratio at the conclusion of the operation.

EVALUATION OF THE ANESTHETIC

In table 5 an attempt has been made to evaluate the quality of the anesthesia. At the conclusion of each operation the operating surgeon was requested to state his opinion of the anesthetic for that particular case. The opinions expressed show that in about 86 per cent of the cases the anesthesia was entirely satisfactory, while in slightly less than 14 per cent it was thought to be only fair or poor.

BLOOD PRESSURE CHANGES DURING AVERTIN ANESTHESIA

In the entire number of cases, careful recordings were made of variations in blood pressure, both systolic and diastolic, as well as changes in the pulse and respiration during the course of the operation. In each case a basal blood pressure reading was taken before the administration of the avertin. There was considerable variation in this initial pressure among the different patients, the highest systolic reading being 210 mm. of mercury and the lowest 72, with an average systolic pressure of 120. Of the diastolic recordings, the highest that was noted was 140 and the lowest 20, with an average diastolic pressure of 72. After the administration of the avertin it was ordinarily noticed that there was a moderate decline in pressure during the first fifteen or twenty minutes; the pressure then gradually rose again, and at the conclusion of the operation was approximately at the preoperative level. In most

TABLE 6.—*Stimulants During Operation*

Stimulants	Number	Per Cent
None	360	83.77
Caffeine	47	11.00
Ephedrine	9	2.09
Both	14	3.14
	430	100
Intravenous dextrose		7
Blood transfusion		5

cases this preliminary drop in blood pressure was not sufficient to cause concern, and there were no attendant objectionable symptoms such as cyanosis or marked changes in the pulse. In case the drop in pressure was extraordinary or tended to be prolonged, it was found that this could be satisfactorily counteracted by the use of ephedrine or epinephrine. In general, it seemed that the administration of some inhalant, such as ether, nitrous oxide or carbon dioxide, aided considerably in bringing up a lowered blood pressure. Table 6 shows the incidence of the use of the various stimulants during the course of the operation. The cases noted in which intravenous dextrose or blood transfusion was required were cases in which the nature of the operation made these expedients necessary, and it was through no possible fault of the anesthetic that they were required. Likewise, the rather large number of cases in which caffeine was given is not a true index of the actual necessity for stimulation consequent on the anesthetic. It was more or less customary at the conclusion of the operation, if the patient was still profoundly narcotized, to administer an ampule of caffeine in order to shorten somewhat the postoperative reaction time. On the whole, my experience would not tend to show that the fall in blood pressure

from the use of avertin was highly objectionable, and it certainly does not seem comparable either in magnitude or as a cause for alarm with the changes in blood pressure that occur during the use of spinal anesthesia. After the administration of the avertin, blood pressure readings were taken at ten minute intervals during the course of the operation. As stated before, the maximum fall in pressure usually occurred from ten to thirty minutes after the introduction of the avertin, and these changes may be summarized as follows: Of the 430 cases followed, in 17, or 4 per cent, there was no initial change in systolic blood pressure. In 357 cases, or 83 per cent, there was a decline in systolic pressure, and in 56 cases, or 13 per cent, there was an actual initial rise in pressure. In the cases showing a decline in systolic pressure the average decrease amounted to —28 mm. of mercury, or a drop of 23 per cent, while

TABLE 7.—*Changes in Blood Pressure*

			Number Cases	Per Cent	Average Amount, Mm. Hg.	Per Cent	Total Average, Mm. Hg.	Per Cent
Systolic	Initial	No change	17	4	....	....		
		Increase...	56	13	+28	+23	−20	−17
		Decrease..	357	83	−23	−23		
	Final	No change	39	9	....	....		
		Increase...	163	38	+ 2	+ 1.7	− 5	− 4
		Decrease..	228	53	− 2	− 1.7		
Diastolic	Initial	No change	34	8	....	....		
		Increase...	91	21	+17	+24	−10	−14
		Decrease..	305	81	−19	−27		
	Final	No change	65	15	....	....		
		Increase...	189	44	+15	+21	+0.3	+0.4
		Decrease..	176	41	−15	−21		

those showing a rise in systolic pressure showed an average increase of + 28 mm. of mercury, or a rise of 23 per cent. The total average initial systolic change amounted to — 20 mm. of mercury, or a drop of 17 per cent. Regarding the initial change in diastolic pressure, of the 430 cases there was no initial change in 34, or 8 per cent. In 305 cases, or 71 per cent, there was a decrease in pressure and in 91, or 21 per cent there was an increase. The amount of these changes is as follows: The average decrease for the 305 cases was — 19 mm. of mercury or a 27 per cent fall, while the average increase in the 91 cases showing an initial rise was + 17 mm. of mercury, or a 24 per cent increase. This gave a total average initial change of — 10 mm. of mercury or a fall of 14 per cent. At the conclusion of the operation the following changes in pressure were noted: Of the 430 cases, the systolic pressure was at the preoperative level in 39, or 9 per cent. In 228, or 53 per cent, it was still below the preoperative level, while in 163 cases, or 38 per cent, it was above the basal reading. Of the cases in which there was a final decrease in systolic pressure, the average

amounted to — 2 mm. of mercury, or 1.7 per cent. Of those show-
ing an increase, the average increase was + 2 mm. of mercury, or 1.7
per cent, while the total average systolic change was — 5 mm. of mer-
cury, or a 4 per cent drop. Final diastolic changes were as follows: Of
the 430 cases, 65, or 15 per cent, showed no change; 176 cases, or 41
per cent, showed a decline and 189 cases, or 44 per cent, showed an
increase. Of those showing a decrease, the average decline was — 15
mm. of mercury, or 21 per cent, while the average increase in those
showing a rise was + 15 mm. of mercury, or 21 per cent, and the total
average diastolic change was negligible. Table 7 summarizes these
changes in blood pressure.

CHANGES IN PULSE AND RESPIRATION

Changes in the pulse rate following the administration of avertin
were also studied. Of the 430 cases, 30, or 7 per cent, showed no

TABLE 8.—*Changes in Pulse and Respiration*

		Number Cases	Per Cent	Average Number Beats	Total Average
Pulse	Increase...............	262	61	+19 ⎱	
	Decrease........	138	32	—16 ⎰	+7
	No change............	30	7	....	
Respiration	Increase........	305	71	+ 9 ⎱	
	Decrease........... ...	60	14	— 4 ⎰	+6
	No change.....	65	15	....	

change in pulse rate after the administration; 138 cases, or 32 per cent,
showed a decrease in the pulse rate, while 262, or 61 per cent, showed
an increase. The average increase in those showing an elevation in
pulse rate was + 19. The average decrease in those showing a drop
was — 16, while the total average pulse change was + 7. The changes
in respirations were: Three hundred and five cases, 71 per cent, showed
an increase in the respiratory rate; 60 cases, 14 per cent, showed a
decrease in the respiratory rate, while 65, 15 per cent, showed no
change. The average increase in the respiratory rate of those showing
a rise was + 9, and the average decrease in those showing a decline
was — 4. The total average change in respiratory rate was +6.

NAUSEA AND VOMITING

The incidence of postoperative nausea and vomiting is of interest.
In 267 cases, or 62 per cent, nausea and vomiting were entirely
absent. In 163 cases, or 38 per cent, there were some nausea and
vomiting after operation. For the most part these were very transient
and ordinarily could be ascribed to the operation itself rather than to
the anesthetic, and in none of the cases were nausea and vomiting
greatly prolonged, as one occasionally sees after deep ether narcosis.

REACTION TIME

Of particular interest was the time required for reaction. Table 9 shows in a statistical way the time interval between the conclusion of the operation and the time when reaction took place. It will be noted that in a small group of 10 cases the patients reacted immediately after the operation, while approximately 23 per cent of the patients reacted in less than one hour. The largest group was composed of 204 patients, or 47 per cent of the total number. These patients reacted between one and three hours, whereas the next largest group reacted between three and six hours, and a comparatively small number required more than six hours for reaction. The longest reaction time recorded was eighteen hours, and the second longest period fifteen hours. Further mention of the two patients who died without reacting will be made

TABLE 9.—*Reaction Time*

Time	Number	Per Cent
Immediate..	10	2.48
2 to 15 min.......	44	10.25
15 min. to 1 hr....	45	10.56
1 to 3 hr...............	204	47.52
3 to 6 hr................	104	24.22
6 to 12 hr............	16	3.73
Over 12 hr..........	5	1.24
	423	100
Died without reacting....	2	
	420	
Average reaction time—2½ hr.		

later. The average reaction time as computed for all of the cases amounted to two and one-half hours. At the present time, I am trying the effect of withdrawal of the residual avertin solution from the rectum at the conclusion of the operation. Following this, a rectal instillation of oil is given. While no definite data are as yet available on the results, there is some evidence to show that the reaction time can be further shortened in this manner. After reacting, the patients were ordinarily drowsy for several hours longer but could be readily awakened for the administration of fluids. In our opinion, there was no increase in the necessity for postoperative catheterizations. A striking and advantageous feature was the subsequent amnesia for this postoperative period.

POSTOPERATIVE COMPLICATIONS

A complete tabulation of all complications arising during convalescence was made. Table 10 lists the major nonfatal complications which were found and also the time of their appearance. Of especial interest in this connection is the group of cases in which postoperative pulmonary complications developed which might be attributed to the

anesthetic.   On the assumption that such complications will make their
appearance within five days after operation, the cases in which there
were pulmonary complications that might be charged to avertin are
marked with an asterisk.   The first 4 cases in the table fall into this
category.   They consisted of 2 cases of bronchitis, 1 of pleurisy and 1
of bronchopneumonia.   All of the patients recovered under the usual
treatment.   Case 257443, in which a nephrectomy was done for renal
tuberculosis, was that of a patient with other associated tuberculous

TABLE 10.—*Postoperative Complications*

Case No.	Age	Sex	Operation	Anesthetic Combination	Complications	Time of Development After Operation
266266*	29	M	Inguinal herniotomy and orchidopexy	110 mg. per Kg. and gas	Pneumonia	2nd day
265910*	50	M	Spinal fusion	110 mg. per Kg. alone	Pleurisy	2nd day
276750*	43	M	Cholecystectomy and appendectomy	110 mg. per Kg. and gas	Bronchitis	4th day
265890*	29	F	Cholecystectomy and appendectomy	110 mg. per Kg. and ether	Bronchitis	3rd day
250033	40	F	Cholecystectomy and appendectomy	110 mg. per Kg. and gas	Pulmonary infarct or bronchopleurisy at base of right lung	2 wk.
261776	37	F	Cholecystectomy	110 mg. per Kg. and ether	Respiratory paralysis	Immediately
255423	75	M	Colostomy for carcinoma of rectum	110 mg. per Kg. and gas	Heart block (advanced myocarditis)	2nd day
257443*	84	F	Nephrectomy for tuberculosis	115 mg. per Kg. and gas	Bronchopneumonia? tuberculous	2nd day
269856	47	M	Cholecystogastrostomy for carcinoma of pancreas	110 mg. per Kg. alone	Pleurisy with effusion	11th day
278866*	33	M	Drainage of appendiceal abscess	110 mg. per Kg. and gas	Respiratory paralysis	2nd day
235818	36	M	Abdominal sympathectomy	130 mg. per Kg. alone	Postoperative mania (psychogenic)	For 2 wk.

lesions, and the pneumonia, which developed on the second postopera-
tive day, was thought possibly to be a tuberculous pneumonia.   The
acute condition cleared up promptly, but the patient was placed on the
usual regimen ordinarily prescribed for patients with pulmonary tuber-
culosis.   Case 270866 must be included among the pulmonary com-
plications.   This patient, shortly after being returned to the ward
following operation, had a temporary respiratory arrest, for no clear
reason.   Under appropriate treatment he was resuscitated, and the
remainder of the convalescence was without event.   In case 261776
likewise, temporary paralysis occurred.   Here, however, it was thought
that this was due to a slip in the ward routine.   The patient, who
had had a preliminary dose of morphine and hyoscine before the
administration of the avertin, was returned to the ward following

operation in good condition but still deeply narcotized. On her return, through a misunderstanding of orders, the nurse in charge at once administered ¼ grain of morphine subcutaneously. Shortly after this there was a cessation of respiration, although the pulse remained practically normal. Artificial respiration was instituted at once, and after a period of about fifteen minutes normal respiration again took place, and there was nothing further to mar the convalescent period. This undoubtedly was due to an error in management, and it was felt that had the additional morphine not been given this complication could have been averted.

In the entire series there was no evidence of rectal irritation or ulceration from the use of avertin in any case. No case was discovered in which there was bleeding or discharge from the rectum, and no symptoms such as rectal pain or discomfort were encountered following the use of avertin. This we attribute to the fact that great care was exercised in the preparation of the solution, as it seems to have been satisfactorily proved that the early cases in which such complications ensued were undoubtedly due to the fact that either decomposed preparations or solutions of improper p_H value were used.

Likewise, there was no evidence that repeated administrations of the drug were attended with additional danger. Several instances occurred in the series in which avertin was used repeatedly without ill effect. One man in the course of a year had nine plastic operations, all done with avertin, and a woman with gallstones, who refused operation, received six full sized doses in a period of two weeks for the control of intolerable pain.

DEATHS

In the 430 cases, there were 22 deaths, or a mortality of 5.1 per cent. It can be readily seen from table 11 that in most instances the deaths were due to causes other than the anesthetic, and for the most part the fatal issue took place a considerable time after the operation was performed. The cases in which the anesthetic may have been or probably was a factor have been marked with an asterisk and might be mentioned individually. Case 272390 undoubtedly must be classified as one of death due to avertin. This patient had a laparotomy for what proved to be an inoperable carcinoma of the stomach with abdominal carcinomatosis. The operation consisted of exploration only. He left the operating room in satisfactory condition but failed to react and died suddenly five hours later. Autopsy showed no positive cause for the sudden death. The most striking observation was a rather intense pulmonary edema.

In case 263327 the patient was a frail little woman with an adenomatous goiter and a damaged myocardium. It will be noted that

the avertin dosage was considerably decreased below the average dose used in the series, and the patient awakened promptly at the conclusion of the operation. However, bronchopneumonia developed, proved by roentgen examination, probably on the basis of postoperative atelectasis, and this proved to be fatal in twenty-four hours.

TABLE 11.—*Number of Deaths*

Case No.	Age and Sex	Operation	Anesthetic Combination	Cause of Death	Time of Death After Operation
259041	48 F	Ventral hernia and fecal fistula	120 mg. per Kg. alone	Generalized sepsis	7 wk.
269951	47 F	Nephrectomy for calculus, pyonephrosis	110 mg. per Kg. alone	Empyema bronchopleural fistula (16th day)	18th day
275073	62 M	Anterior gastro-enterostomy for carcinoma of stomach	120 mg. per Kg. and gas	Renal insufficiency	13th day
254336	25 F	Duodenojejunostomy	110 mg. per Kg. alone	Ulceration at anastomosis site and hemorrhage	8th day
263643	33 M	Multiple compound fracture of mandible and maxilla	130 mg. per Kg. alone	Fat embolism of lung	1 hr.
273841	46 M	Lobectomy of upper and middle lobes for carcinoma of bronchus	110 mg. per Kg. and gas	Pulmonary gangrene	2 days
277839	38 M	Ligation of internal jugular and ablation of sigmoid sinus for sigmoid sinus thrombosis	110 mg. per Kg. and gas	Cavernous sinus thrombosis	13 days
257273	18 M	Reamputation of thigh for septic knee	110 mg. per Kg. and gas	Bronchopneumonia	33 days
255786	34 F	Left nephrolithotomy	110 mg. per Kg. and gas	Pyelonephritis	3 wk.
267018	27 F	Splenectomy for purpura hemorrhagica	110 mg. per Kg. and gas	Continued hemorrhage	3 days
257655	57 M	Polya resection for gastric ulcer	110 mg. per Kg.	Renal insufficiency and urinary suppression	5 days
270669	23 M	Thigh amputation for tuberculosis of the knee	110 mg. per Kg. alone	Widespread tuberculosis	41 days
270308	69 F	Billroth II for carcinoma of stomach	110 mg. per Kg. alone	Intestinal fistula	15 days
191783	65 M	Sublingual abscess, endothermy	110 mg. per Kg. alone	Septicemia	6 days
272390*	49 M	Exploratory laparotomy for carcinoma of stomach with carcinomatosis	110 mg. per Kg. and gas and ether vapor	Did not react	5 hr.
252395	33 F	Ureterostomy for carcinoma of bladder	110 mg. per Kg. and gas and ether vapor	Metastatic carcinoma and pyelonephritis	22 days
263327*	55 F	Thyroidectomy for adenomatous goiter	80 mg. per Kg. and gas	Atelectasis and bronchopneumonia	24 hr.
278395*	57 M	Gastrostomy for carcinoma of esophagus and tracheo-esophageal fistula	110 mg. per Kg. alone	Extensive carcinoma; did not react	24 hr.
278243	57 M	Polya resection for carcinoma of stomach	110 mg. per Kg. alone	Peritonitis	14 days
216624*	56 M	Metastatic carcinoma of neck glands (primary in tongue); excision of glands with ligation of internal carotid artery	110 mg. per Kg. and gas	Right hemiplegia (2nd day after operation; bronchopneumonia (5th day after operation)	8th day
279539	52 F	Cholecystostomy for carcinoma of gallbladder with stones and empyema of gallbladder	110 mg. per Kg. and ether	Duodenal fistula (carcinoma)	29th day
273282	53 F	Bilateral ureteral transplant and cystectomy for carcinoma of bladder	110 mg. per Kg. alone	Cardiac failure	2nd day

In case 278395, the patient was an extremely emaciated man who had a cancer of the esophagus complicated by a tracheo-esophageal fistula. While his condition was desperate, a gastrostomy seemed to be clearly indicated. This operation is ordinarily performed under local anesthesia, but in this particular case avertin was chosen in order that a satisfactory examination of the trachea with biopsy might be carried out. This patient also failed to react from the avertin narcosis and died twenty-four hours later. An autopsy was not obtained.

In case 216624, the patient was a man with an extensive metastatic carcinoma of the cervical glands for which a radical resection was done. In the course of the operation it became necessary to ligate the internal carotid artery with the unfortunate consequence that a hemiplegia developed on the second postoperative day, and on the fifth day there was definite evidence of bronchopneumonia from which the patient died on the eighth day.

In case 273841, the patient was a man with carcinoma of the right primary bronchus. In doing a lobectomy of the upper and middle lobes, the main pulmonary artery was accidentally tied, which accounted for the gangrene of the lower lobe, which proved to be fatal on the second postoperative day.

Considering these two tables together, there were 8 cases of post-operative pulmonary complications, for the occurrence of which the anesthetic probably played a part. This gives a percentage of postoperative pulmonary complications of 1.9 per cent. Of these post-operative pulmonary complications, there were 4 frank pneumonias, giving a percentage of 0.9 per cent for the entire series. Of the postoperative pneumonias, 2 were fatal, giving a percentage of 0.5 per cent for the entire series, and of 50 per cent for the postoperative pneumonias.

SUMMARY

The results from the use of avertin in this series of selected cases were on the whole highly satisfactory. The easy induction was one of the outstanding features and one that made avertin particularly agreeable to the patients. Avertin proved to be of especial value in operations on the head and face, in which many times it was possible to dispense completely with cumbersome apparatus such as gas masks or ether cones. Perhaps its sphere of greatest value was in abdominal surgery where, when combined with some supplemental anesthetic agent, it aided considerably in enhancing muscular relaxation. We are not prepared to advocate it as having any decided advantages in thyroid surgery. While it is admirably suited to the "steal" type of operation, it has not seemed that the quality of the anesthesia in these cases was importantly better when avertin was employed, and there are objections

both theoretical and actual to a prolonged period of somnolence after operation in this type of case. In such cases it seems particularly desirable to avoid abolition of the cough reflex, when mucus is apt to accumulate in the throat and attendant laryngeal edema is often present.

CONCLUSIONS

1. A representative group of 430 surgical cases in which avertin was employed for anesthesia or basal narcosis has been analyzed.

2. The quality of surgical anesthesia produced by avertin unassisted or supplemented by gas or ether in most cases is entirely satisfactory. The induction from the standpoint of the patient is probably less unpleasant than that attendant on any other form of anesthetic.

3. In this series some form of supplemental anesthetic, such as nitrous oxide and oxygen or ether, was required in approximately 70 per cent of the cases, the operation in the remaining 30 per cent being performed without reinforcement.

4. While there was usually a preliminary fall in both systolic and diastolic blood pressure, this did not seem to be sufficient to cause alarm, and at the conclusion of the operation the pressure had practically reached the preoperative level. Falls in blood pressure were satisfactorily combated with ephedrine or epinephrine.

5. When nitrous oxide and oxygen were employed as a supplemental agent, the percentage of oxygen in the mixture could be increased to practically twice the amount possible when used with nitrous oxide alone. Likewise, if ether was used to supplement the avertin, the total quantity employed during the operation was considerably less than would have been required for straight ether anesthesia.

6. The average reaction time was two and one-half hours. The majority of the patients reacted between one and three hours, while about 23 per cent reacted in less than one hour.

7. Of the 22 operative deaths occurring in the series, only 4 seemed to have any definite relation to the type of anesthesia. In the entire series there were only 8 cases of postoperative pulmonary complications which seemed in any probability attributable to the avertin. Of these 8 cases of postoperative pulmonary complications, 4 were of pneumonia, and of these 4 postoperative pneumonias, 2 were fatal.

8. In order to avoid unnecessary dangers, it seems that considerable care should be exercised in selecting cases. If this is done, avertin, in my opinion, is not only a safe but an important addition to the anesthetic armamentarium.

SPLENECTOMY IN THE TREATMENT OF HEMORRHAGIC PURPURA

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LOS ANGELES

Thrombocytopenic purpura hemorrhagica is characterized clinically by pathologic hemorrhage, ranging from a massive loss in the acute form, usually with a rapid termination, to the milder form, lasting for years. The blood platelets or thrombocytes show marked reduction. Until recently, splenectomy in the fulminating form was considered contraindicated and futile. Killins,[1] Reuben and Claman [2] and others, however, have reported recoveries from the acute form following splenectomy.

The success of splenectomy in the majority of cases of the chronic form is conceded. A certain number of failures are reported, and these are difficult to explain. Giffin and Holloway [3] found no clinical or hematologic improvement in 4 of their 28 cases. Spence,[4] out of 101 cases abstracted, found 15 per cent with a return of symptoms.

The commonly accepted theory for the successful results after splenectomy regards the spleen as abnormally destructive to platelets, producing thrombocytopenia and its sequelae. The whole reticulo-endothelial system is diseased, and the spleen exerts the greatest destructive influence. Better results follow splenectomy performed on persons with the largest spleens and seem to corroborate this idea. Removal of the spleen usually is followed in a few hours by a marked rise in the blood platelets, and rarely is there postoperative bleeding. The great bulk of reticulo-endothelial tissue is represented by the spleen, and its extirpation usually is adequate. Return of symptoms theoretically should suggest increased activity or hyperplasia of the remaining reticulo-endothelial tissue.

1. Killins, W. A.: Acute Thrombocytopenic Purpura Cured by Splenectomy, J. A. M. A. **92**:1832 (June 1) 1929.

2. Reuben, M. D., and Claman, L.: Splenectomy in Acute Thrombocytopenic Purpura Hemorrhagica, Arch. Pediat. **45**:84 (Feb.) 1928.

3. Giffin, H. Z., and Holloway, J. K.: A Review of Twenty-Eight Cases of Purpura Hemorrhagica in Which Splenectomy Was Performed, Am. J. M. Sc. **170**:186 (Aug.) 1925.

4. Spence, A. W.: Results of Splenectomy for Purpura Hemorrhagica, Brit. J. Surg. **15**:466 (Jan.) 1928.

That the return of symptoms is often due to an unnoticed accessory spleen is suggested by Morrison, Lederer and Fradkin.[5] They described a patient whose spleen was removed, but in whom a small accessory spleen was allowed to remain. Improvement was immediate but transient, and in a year the patient was bleeding again. They suggested hypertrophy of the remaining accessory spleen as an explanation. They believe the relative frequency of supernumerary spleens, often situated in aberrant abdominal foci, can account for many unsatisfactory results. They enjoin a careful search for accessory splenic tissue during splenectomy.

On the other hand, many patients show clinical improvement, with relief from hemorrhagic symptoms, and still fail to show satisfactory improvement in the hematologic findings. The platelets may remain low, the bleeding time prolonged, the tourniquet test positive and the blood clot nonretractile and still the patient will show no spontaneous ecchymosis, oozing gums or other hemorrhage from the mucous membranes.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis between purpura hemorrhagica and other blood dyscrasias when typical is comparatively sure, save in some fulminating types. Aplastic anemia, in the bleeding stage, is characterized by extreme anemia, marked leukopenia and reduction of the granulocytes, with no splenomegaly. Acute leukemia, especially if in the aleukemic stage and without peripheral adenopathy, may present difficulties. There may be splenomegaly, but the differential count of the white cells will usually show immature lymphocytes and lymphocytosis. In acute purpura hemorrhagica, the red count at the onset is not usually markedly reduced, anemia occurring in proportion to the loss of blood. The hemophilic person shows marked prolongation of the coagulation time and a normal bleeding time.

ATYPICAL HEMORRHAGIC DISEASE

Recent literature has been instructive in showing the many atypical cases of hemorrhagic disease that occur. Glanzman,[6] Rothman and Nixon,[7] Minot[8] and others described a familial type of purpura hemorrhagica without thrombocytopenia. A normal platelet count is associated

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5. Morrison, M. D.; Lederer, M., and Fradkin, W. Z.: Accessory Spleens, Their Significance in Essential Thrombocytopenic Purpuric Hemorrhagica, Am. J. M. Sc. **176**:672 (Nov.) 1928.

6. Glanzman, E.: Hereditäre hämorrhagische Thrombasthenie, Jahrb. f. Kinderh. **88**:1 and 113, 1918.

7. Rothman, P. E., and Nixon, N. K.: Familial Purpura Hemorrhagica Without Thrombopenia, J. A. M. A. **93**:16 (July 6) 1929.

8. Minot, G. R.: A Familial Hemorrhagic Condition Associated with Prolongation of the Bleeding Time, Am. J. M. Sc. **175**:301 (March) 1928.

peculiarly with a prolonged bleeding time, a nonretractile clot and a positive tourniquet test. The patients have all the clinical phenomena of purpura hemorrhagica. The platelets in this condition are believed to be qualitatively defective; hence the term "thrombasthenic" purpura in distinction to thrombocytopenic purpura.

In addition to one of the familial types, Giffin [9] reported another case, in a patient aged 9, with all the features of hemorrhagic purpura except thrombocytopenia. Bleeding from the mucous membranes occurred, with a prolonged bleeding time and a nonretractile clot but a normal number of platelets. Splenectomy was done, without the usual prompt improvement such as follows typical purpura hemorrhagica.

Sweeney [10] reported an atypical case in which the diagnosis was extremely difficult. Clinically, the patient had marked hemorrhages, but despite a greatly prolonged bleeding time the platelets were not reduced. The white cells were normal. He was given numerous transfusions of blood, but failed to improve, and as a last resort a splenectomy was done. There was a slight transient rise in the white cells, but no increase in the platelets and no improvement clinically. The patient died about six months later.

Kennedy [11] described the case of a child aged 4, with a prolonged bleeding and coagulation time, decreased platelets, intense anemia and slight leukocytosis. A splenectomy was done without improvement. Two months later tonsillectomy was followed by excessive hemorrhages and death. Necropsy revealed an aplastic bone marrow. The patient had an atypical aplastic anemia. Splenectomy in the cases reported by Giffin and Kennedy for familial thrombo-asthenic purpura hemorrhagica has not given the satisfactory results obtained in pure thrombocytopenic purpura. Little and Ayres [12] reported a death following splenectomy in a case of hereditary hemorrhagic purpura with a normal platelet count.

The most careful scrutiny of all patients with hemorrhagic disease is indicated before splenectomy is resorted to. Many cases are not typical, and the differential diagnosis is most difficult. In borderline cases with no improvement, splenectomy is perhaps justifiable if the hemorrhage is unrelieved by transfusion and death seems otherwise inevitable. The cases of acute bleeding, as described by Kennedy [10] and Killins,[1] were of this type. In the chronic type of bleeding with

9. Giffin, H. Z.: Unusual Types of Hemorrhagic Disease, Am. J. M. Sc. **175**:44 (Jan.) 1928.

10. Sweeney, J. S.: Chronic Aplastic Anemia and Symptomatic Purpura Hemorrhagica Probably Due to Benzol Poisoning, Am. J. M. Sc. **175**:317 (March) 1928.

11. Kennedy, R. L. J.: Diseases of Children Benefited by Splenectomy, J. A. M. A. **91**:874 (Sept. 22) 1928.

12. Little, W. D., and Ayres, W. W.: Hemorrhagic Diseases, J. A. M. A **91**:1251 (Oct. 27) 1928.

ecchymoses, bruising and moderate anemia we believe that it is better
to postpone splenectomy unless the following requisites are met: (1)
splenomegaly; (2) thrombocytopenia; (3) prolongation of the bleeding
time; (4) nonretractility of the blood clot; (5) positive tourniquet test
showing decreased capillary resistance; (6) normal coagulation time
and (7) a normal or slightly increased leukocyte count.

The following case illustrates the clinical recovery following sple-
nectomy in typical chronic hemorrhagic purpura, without, however, a
hematologic recovery.

REPORT OF A CASE

Miss M. S., aged 36, reported that at the age of 14 she noticed numerous spots
on the legs about the size of a dime or greater, occurring without any bruising
or injury. She was nicknamed "Spotty" by her playmates. At the age of 16 she
was bitten on the arm by a mosquito, and a black and blue spot about 2 inches
(5 cm.) in diameter developed at the site. At 19 she had an acute, severe pain
in the lower part of the abdomen and fainted. In college she noticed that the
discharge during her menstrual periods became profuse. Occasionally, a severe
spontaneous vaginal hemorrhage developed.

In 1920, tonsillectomy was advised in the belief that the purpura was possibly
due to infection. She lost a great deal of blood, and it was thought she would not
live. Transfusion of blood was not resorted to, and the bleeding finally was
stopped by clamps.

In October, 1922, she had another acute attack of abdominal pain associated
with vomiting, believed to be acute appendicitis. She was seen by a physician,
and for the first time was told that she had purpura hemorrhagica. Splenectomy
had not yet been established in America as accepted treatment, and she forsook
regular medical care for osteopathy. Brill and Rosenthal's [13] paper, in 1923,
brought splenectomy a more generalized recognition, although Kaznelson [14] had
reported the first case in 1916.

In 1923, she had a severe uterine hemorrhage.

In the summer of 1928, she had another attack of severe abdominal pain, during
which she became very faint and weak. There was no external bleeding, but she
became so anemic that she was given her first transfusion of blood. About this
time, she first noticed a little oozing of blood from the gums and observed blood
spots on her pillow in the morning.

In August, 1929, she was seized with griping abdominal pain, and vaginally
passed several clots of blood. She had marked bleeding from the gums, the
bleeding continuing for thirty-six hours. The vaginal bleeding finally was stopped
by packing. She was seen at the office on Aug. 27, 1929. The skin was markedly
pale, the mucous membranes washed out. A number of ecchymoses were present
on the arms and legs. The spleen was enlarged two fingerbreadths below the
costal margin. Changes in the blood typical of chronic thrombocytopenic hemor-
rhagic purpura were present and splenectomy was advised. She had another attack

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13. Brill, N. E., and Rosenthal, N.: Treatment by Splenectomy of Essential
Thrombocytopenia (Purpura Hemorrhagica), Arch. Int. Med. **32**:939 (Dec.)
1923; The Curative Treatment by Splenectomy of Chronic Thrombocytopenic Pur-
pura Hemorrhagica, Am. J. M. Sc. **166**:503 (Oct.) 1923.

14. Kaznelson: Wien. klin. Wchnschr. **29**:1451, 1916.

of severe pain in the lower part of the abdomen and menorrhagia the next month; after its cessation she was admitted to St. Vincent's Hospital on November 1.

She was bleeding from the gums, and numerous suggillations were present on the body. The site of a hypodermic injection became swollen and discolored. The

TABLE 1.—*Changes in the Blood in Our Case of Purpura Hemorrhagica*

	Red Blood Cells in Millions	Hemoglobin, per Cent	Leukocytes in Thousands	Polymorphonuclear Leukocytes, per Cent	Platelets in Thousands	Bleeding Time, Minutes	Clot Retractility	Tourniquet Test
Before splenectomy								
90 days.........	4.4	25	9.7	61	...	..	Negative	Positive
13 days..	3.0	20	6.4	74	50	20	Negative	
8 days.........	3.1	25	5	..	...	20	....	Positive
8 days.........	Direct transfusion—500 cc. whole blood							
4 days.........	3.5	30	4.6	79	80			
2 days.........	Direct transfusion—500 cc. whole blood							
2 days.........	3.8	34	5	78	150	14		
	Splenectomy followed by transfusion—500 cc. blood							
After splenectomy								
1 day.........	4.4	42	57	94	177			
2 days.........	...	..	55	96	160	4.5	Present	Negative
4 days.........	4.2	39	33 ..	87				
6 days.........	4.2	38	25	86	310	..	Present	Negative
9 days.........	4.2	41	16.5	80	380			
15 days.........	4.4	46	17	78	270	4		
20 days.........	4.4	45	14	79	240			
27 days.........	4.4	50	12.7	80	250	4		
6 months......	3.8	..	15	64	190	5		
9 months......	3.9	35	19.1	58	...	3		
11 months......	5.8	59	16	52				
13 months......	4.9	67	18	68				
18 months......	4.7	65	15	58	29	2.5	Absent	Positive

TABLE 2.—*The Main Changes in the Blood in Hemorrhagic Disease*

	Purpura Hemorrhagica		Aplastic Anemia	Acute Leukemia	Hemophilia
	Acute	Chronic			
Splenomegaly..............	Not usually	Present	Not present	Variable	Not present
Anemia...................	Proportionate to bleeding	Proportionate to bleeding	Marked anemia before bleeding	Proportionate to bleeding	Variable, depends on loss of blood
White blood cells...........	Normal or increased	Normal or increased	Marked leukopenia	Leukemic normal or aleukemic	Normal
Differential blood study....	Normal	Normal	Granulocytopenia	Atypical immature lymphocytes	Normal
Bleeding time..............	Increased	Increased	Increased	Increased	Normal
Blood platelets.............	Reduced	Reduced	Reduced	Reduced	Normal count
Coagulation time..........	Normal	Normal	Normal	Normal	Markedly prolonged
Heredity...................	May be familial type	May be familial type	Negative	Negative	Familial

bleeding time was twenty minutes, the platelet count, 50,000. She was given a transfusion of whole blood on November 10 and again on November 12, with only slight improvement in the bleeding time. Splenectomy was done on November 14, followed by an immediate transfusion, which was given as a precautionary measure, as there was no postoperative bleeding from the wound.

The pathologic report by Dr. E. M. Hall was as follows:

"The spleen is about two and one-half times normal size, and measures 15 by 9 by 5 cm. The capsule is smooth. There is a deep fissure near the upper third. The cut surface has a meaty appearance, the marking is indistinct, and the consistency firm.

"Sections stained with Giemsa show moderate, diffuse fibrosis, marked conges·tion, marked hypertrophy and hyperplasia of the endothelial cells of the venous sinuses. The venous spaces also contain a few polymorphonuclear leukocytes and an occasional eosinophil and normoblast. The diagnosis is chronic purpura hemorrhagica."

Clinically, there was a complete disappearance of oozing from the gums and purpuric spots the day after splenectomy. The blood changes are shown in the chart and table. About the sixth postoperative day, the patient complained of a rheumatic pain in her left shoulder, and signs of fluid gradually developed in the left pleural cavity. On the fourteenth postoperative day, a temperature of 101 F. developed. The chest was tapped on December 1, and 1,500 cc. of red turbid fluid was removed. This proved to be sterile. Following this the fever dropped, and there was no recurrence. She was discharged in good condition one month after splenectomy.

<p align="center">COMMENT</p>

This case illustrates the rather typical response of the blood picture to splenectomy. A tremendous leukocytosis, due to proliferation of the granular leukocytes, was found the day after splenectomy. This slowly decreased, but a year later the white cell count was still elevated. The frequency with which this is found after splenectomy for purpura hemorrhagica suggests the existence of a leukotoxin in addition to the supposed lysin that destroys the platelets. The persistent leukocytosis is unexplainable. Evans,[15] in reporting the blood changes following splenectomy, found no persistent leukocytosis. The white cells were usually normal within a month.

The slower rise in platelets, reaching the maximum about the eighth day after operation, is characteristic. The response, however, was moderate, the count failing to rise to the frequent level of from 500,000 to 1,000,000.

The immediate return to normal of the bleeding time after splenectomy was coincident with the rise of platelets. Over a period of a year and a half since the operation, there has occurred a gradual reduction of the platelets, but despite this, the clinical improvement has continued. There has been a gain in weight and strength. The patient is again teaching.

The end-result of the splenectomy as seen a year later was a clinical cure, but only moderate hematologic improvement. The so-called essential factor in the production of the disease, thrombocytopenia, had

15. Evans, W. H.: The Blood Changes After Splenectomy in Splenic Anemia, Purpura Hemorrhagica and Acholuric Jaundice, with Special Reference to Platelets and Coagulation, J. Path. & Bact. **31**:815 (Oct.) 1928.

reappeared, but the usual sequel, pathologic hemorrhage, had not. The blood clot again failed to retract; there was a shower of petechiae on application of the tourniquet, but no oozing of the gums or menorrhagia. Again, atypically and peculiarly, the bleeding time was normal.

That there is an additional factor responsible for the disease other than the thrombocytopenia is indicated by this and other reports. Apparently, clinical hemorrhagic purpura can appear when the platelets are normal in number, as in the "thrombasthenic" type, usually familial. Conversely, a patient may have a marked reduction of the blood platelets without clinical purpura hemorrhagica.

It follows that the sole explanation for the clinical cure of purpura hemorrhagica in the majority of cases by splenectomy cannot be the postoperative elevation of the platelets. It is concomitant with improvement, but the effect of splenectomy is more complex and far-reaching than it has yet been possible to explain.

SUMMARY

The salient facts in the literature concerning so-called chronic essential thrombocytopenic purpura have been reviewed. A number of atypical cases of unusual hemorrhagic disease have been cited, and the futility of treatment for such cases by splenectomy pointed out. The necessity for a meticulous scrutiny of all hemorrhagic patients to eliminate atypical cases such as "thrombasthenic" purpura is suggested.

A case showing a clinical recovery but a hematologic failure is described. Thrombocytopenia apparently is not the only factor operating in purpura hemorrhagica.

PASSAGE OF CHOLESTEROL THROUGH THE MUCOSA OF THE GALLBLADDER

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For the past number of years the question of the etiology of cholesterosis of the gallbladder has assumed widespread interest.

In a series of 5,000 gallbladders removed at operation, MacCarty,[1] in 1919, found cholesterosis of the gallbladder to be present in 18 per cent of his cases. In 1921, Mayo[2] found cholesterosis in 39 per cent of 1,254 cases of disease of the gallbladder. Mentzer[3] in 1926 published autopsy reports of 612 cases, with an incidence of cholesterosis as high as 38 per cent. In 1929, Illingworth[4] noted cholesterosis in 21 of 100 consecutive gallbladders removed at operation.

Anywhere from 20 to 50 per cent of these cases of cholesterosis were associated with gallstones, usually composed of pure cholesterol.

Cholesterosis, so named by Mentzer[5] in 1925, is a pathologic condition of the mucosa of the gallbladder, consisting macroscopically of tiny yellowish granules lying beneath the epithelium. Microscopically, in a Sudan-stained section, lipoid material may be seen deposited at the bases of the epithelial cells and in the large mononuclear endothelial cells of the stroma. In the majority of cases the subepithelial coat appears thickened by a varying amount of fibrous connective tissue. Very often scattered areas of small round cells may be seen. As a result of the combined fibrosis and the excessive deposits of lipoid material, the so-called "villi" of the mucosa are, as a rule, found to be shortened and thickened, but occasionally may be elongated and bulbous, or even definitely papillomatous in appearance.

1. MacCarty, W. C.: Ann. Surg. 69:131, 1919.
2. Mayo, C. H.: Minnesota Med. 4:1, 1921.
3. Mentzer, S. H.: Surg., Gynec. & Obst. 42:782, 1926.
4. Illingworth, C. F. W.: Brit. J. Surg. 17:203, 1929.
5. Mentzer, S. H.: Am. J. Path. 1:383, 1925.

Virchow first noticed what he considered to be cholesterol in the mucosa of the gallbladder in 1857. Moynihan in 1909 described the macroscopic condition aptly named by MacCarty the "strawberry" gallbladder. It remained for Boyd,[6] however, in 1922, to show that the yellow material found in the wall of the gallbladder in these conditions was undoubtedly cholesterol. He demonstrated that the normal dried mucosa of the gallbladder contained about from 0.5 to 1 per cent of cholesterol, whereas the dried mucosa of the strawberry gallbladder could contain as much as 60 per cent of the substance.

Although various authors have differed in their opinions as to whether inflammation plays any part in the production of cholesterosis, Illingworth [4] has shown experimentally that by feeding rabbits a high cholesterol diet and at the same time producing a chronic cholecystitis, it is possible to obtain a lesion that corresponds closely to that of cholesterosis in the human being.

Mentzer believes cholesterosis to be essentially a metabolic disturbance. Blaisdell and Chandler [7] were able to produce what they believed to be a cholesterosis of the gallbladder by merely administering a high cholesterol diet to animals.

Since 1906, Aschoff [8] has insisted that cholesterol is absorbed by the mucosa of the gallbladder, having proved experimentally that neutral fats and fatty acids could be easily absorbed. However, he was never able to show any direct proof of the absorption of cholesterol. Torinoumi,[9] by reinjecting a measured quantity of bile into gallbladders in which the cystic ducts had previously been ligated and analyzing this bile from seven to thirty-eight days afterward, produced results that tended to confirm Aschoff's belief of the absorption of cholesterol.

Boyd also believes that cholesterol is absorbed by the mucosa of the gallbladder.

Illingworth [4] injected suspensions containing 3,442 mg. of cholesterol per hundred cubic centimeters of bile into the gallbladder of cats, after tying the cystic duct, and showed that under these conditions a part of the cholesterol was absorbed from the gallbladder. It must be remembered, however, that this concentration of cholesterol is about ten times as great as that which normally occurs in the bile in the gallbladder, and that the medium used was an artificial one.

Naunyn,[10] on the other hand, always considered that the cholesterol of the bile was derived from the mucosa of the biliary passages and

6. Boyd, W.: Brit. J. Surg. **10**:337, 1922.

7. Blaisdell, F. E., and Chandler, L. R.: Am. J. M. Sc. **174**:492, 1927.

8. Aschoff: München. med. Wchnschr. **37**:1847, 1906.

9. Torinoumi: Beitr. z. path. Anat. u. z. allg. Path. **72**:456. 1924.

10. Naunyn, B.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:2. 1921.

gallbladder. His opinion, however, was not based on any direct experimental evidence.

The recent experimental work of Elman and Graham [11] seems to favor the latter view, since their evidence indicates that cholesterol is secreted into the bile in the gallbladder.

It may therefore be seen that two main theories exist as to the origin of cholesterol deposited in the wall of the gallbladder in so-called cholesterosis, and in order to understand the condition in which cholesterol plays so important a part, it is necessary at the outset to determine the function of the normal gallbladder in regard to cholesterol.

Most of the workers in the past have experimented with cholesterol in an artificial suspension and in abnormal concentrations. It has been the aim throughout the present work to use as much as possible the normal concentration of cholesterol as found in animal bile.

The purpose of the following experiments is to determine whether cholesterol passes through the wall of the gallbladder from the bile into the blood stream or lymphatics, or, vice versa, from the blood stream into the bile.

TECHNIC

The technic of the experiments was as follows:

A fistula of the common duct was produced in a dog after the method of McMaster.[12] A cholecystectomy was performed; the common duct was cut across, and a cannula was placed in the proximal end. A soft rubber tube was attached to the cannula and led down to a U-shaped tube in the animal's pelvis, whence a second firmer tube was carried through the abdominal wall to a sterile rubber balloon. The object of the U-shaped tube was merely to prevent any tension on the cannula in the common duct. In this way sterile bile from the common duct could be collected when necessary.

In this series of experiments all animals were treated in the same fashion. The operative procedure was carried out as follows:

Under ether anesthesia the dog's abdomen was opened. The cystic duct was carefully isolated and ligated, special care being taken not to include the cystic blood vessels or lymphatics, especially the main trunks of the latter, which course down in the fatty tissue on the inferior aspect of the duct.

The bile was then aspirated through the fundus of the gallbladder by a no. 14 blunt cannula inserted by means of a trocar, which was withdrawn as soon as the gallbladder was pierced. The gallbladder was emptied as completely as possible. Saline was not used to wash out the lumen, as the experience of some experi-

11. Elman, Robert, and Graham, E. A.: The Pathogenesis of the "Strawberry" Gallbladder: (Cholesterosis of the Gallbladder), Arch. Surg. **24**:14 (Jan.) 1932.

12. McMaster: Studies from Rockefeller Institute for Medical Research, 1924, no. 51, p. 107.

menters has shown that such procedure rapidly tends to injure the delicate mucosa. On the other hand, it was found that by ordinary aspiration practically all the bile could be removed and that only a small amount clinging to the mucosa remained.

The amount of bile aspirated was measured and replaced by an equal quantity of bile derived from a fistula of the common duct of another dog, as described. The opening in the fundus was closed by a fine purse-string suture in such a way as to evert the mucosa. A sample of the bile from the common duct was set aside in each case for a quantitative estimation of cholesterol. It was therefore possible to know the exact quantity of cholesterol that was injected into the lumen of the animal's gallbladder. For convenience, this dilute bile from the common duct is termed "A bile."

At the end of twenty-four hours, the animal was killed and the liver, gallbladder and common duct were removed intact. This was done in order to be certain that the cystic blood vessels were not included in the ligature around the cystic duct, and that no accessory bile ducts were communicating with the gallbladder. If either of these errors was found, the experiment was discarded.

If the blood vessels were found intact and the gallbladder was completely isolated, the biliary contents were carefully removed into a small beaker. This was done in such a fashion as not to scrape the mucosa, so that a small portion of the thick inspissated bile was invariably left adherent to the mucosa.

The bile was constantly found to be dark, inspissated and partly precipitated at the end of twenty-four hours. Approximate measurements showed it to be concentrated from two to three times its original volume. This thick viscid bile removed at the end of twenty-four hours is termed the "B bile."

By estimating the total quantity of cholesterol in the A bile and comparing it with the total quantity in the B bile, values are obtained which throw definite light on the cholesterol function of the normal gallbladder during the process of concentration of hepatic bile.

Analysis of the bile cholesterol by the colorimetric method described in the literature was found to be difficult owing to the yellow discoloration present in the extracts. Eventually the method employed was as follows:

A measured quantity of bile was placed into a 100 cc. beaker, and 10 cc. of 20 per cent potassium hydroxide was added. The contents were heated in a water bath for thirty minutes, and 10 cc. of a 30 per cent calcium chloride solution was then slowly added, with constant stirring. Plaster of paris was then added and thoroughly mixed with the contents, which were then dried at 55 C. Extraction was carried out for ten hours in a Soxhlet apparatus, anhydrous ether being used. The ether containing the cholesterol was then poured into a small beaker and the flask rinsed three times with small quantities of fresh ether. After the ether had evaporated at room temperature, the dry residue was extracted with hot chloroform and an appropriate portion of this compared colorimetrically by the Burchard-Lieberman reaction against a standard solution of cholesterol. By the addition of known amounts of cholesterol to the bile, the loss by this method was never more than 6 per cent.

However, as colorimetric estimations of cholesterol are regarded with some doubt by certain investigators, in dogs V, VII and VIII, the estimations of both A and B biles were carried out by the digitonin method exactly as described by

Gardner.[13] Portions of the A biles in these three cases were also determined by the colorimetric method, with the following results:

	Colorimetric	Digitonin
V A	10.86 mg.	8.85 mg.
VII A	15.47 mg.	14.17 mg.
VIII A	6.58 mg.	6.45 mg.

This correlation between the two methods indicates that the colorimetric method used is sufficiently reliable for our purpose. Most investigators have found the colorimetric method to yield slightly higher results than the digitonin method.

EXPERIMENTAL DATA

The results of the experiments are as follows:

Dog I.—After the cystic duct had been ligated, 10 cc. of hepatic bile derived from the biliary fistula of another dog was injected into the gallbladder. Ten cubic centimeters of this bile was found to contain 3.58 mg. of cholesterol. At the end of twenty-four hours, the animal was killed and the gallbladder removed. Only 2 or 3 cc. of thick, dark viscid bile (B bile) was found inside the gallbladder; on analysis, this material was found to contain a total of 5.46 mg. of cholesterol. This represents in twenty-four hours an increase of 1.88 mg., or 52 per cent, of cholesterol in the contents of the gallbladder. Two facts must be noted: in the first place, only 10 cc. of bile was introduced, and secondly, the A bile had a fairly high cholesterol concentration, 35.85 mg. per hundred cubic centimeters of bile.

Dog II.—In a similar way, this animal had 31 cc. of hepatic bile (A bile) containing 7.05 mg. of cholesterol introduced into the gallbladder. At the end of twenty-four hours, estimation of the contents of the gallbladder showed a total of 28.69 mg. of cholesterol, an increase of 21.64 mg., or 307 per cent. In this case three times as much A bile was used as in the previous animal, and in addition the concentration of cholesterol in the A bile was much less, being only 22.75 mg. per hundred cubic centimeters of bile.

Dog III.—Twenty-nine cubic centimeters of hepatic bile, containing 5.69 mg. of cholesterol, was injected into the gallbladder. At the end of twenty-four hours, 14.76 mg. of cholesterol was recovered from the concentrated contents, an increase of 9.07 mg., or 159 per cent.

Dog IV.—Twenty-five cubic centimeters of hepatic bile containing 3.35 mg. was injected into the gallbladder, and at the end of twenty-four hours 16.23 mg. was recovered, an increase of 12.88 mg., or 384 per cent. It may be interesting to note that the concentration of the A bile was quite low, being only 13.42 mg. per hundred cubic centimeters of bile.

13. Gardner, J. A., and Gainsborough, H.: Biochem. J. **21**:130, 1927.

Dog V.—Fifty cubic centimeters of hepatic bile containing 8.85 mg. of cholesterol (as estimated by the digitonin method) was injected into the gallbladder, and at the end of twenty-four hours the thick viscid bile, only about one fourth of its original quantity, was found to contain a total of 29.14 mg. of cholesterol by weight (digitonin). The increase was 20.29 mg., or 229 per cent.

Dog VI.—Twenty-five cubic centimeters of hepatic bile, containing 5.01 mg. of cholesterol, was injected. This bile was allowed to remain in the gallbladder for thirty-eight hours. At the end of this period, extremely thick precipitated bile was found to contain a total of 31.26 mg. of cholesterol, an increase of 26.25 mg., or 524 per cent.

Dog VII.—This animal was treated in a manner similar to the preceding ones with the exception that, for ten days previous to injection, 2 Gm. of cholesterol was added daily to the food in order to raise the cholesterol content of the blood. It has been shown that this content can be easily raised in rabbits by a high cholesterol diet.[4] There is some doubt, however, whether hypercholesterolemia can be produced in omnivorous animals. Lemoine and Gerard[14] and Rothschild and Rosenthal[15] have produced evidence that such hypercholesterolemia can occur. We have found it to be so in the case of dogs. Thus, on feeding two dogs, each weighing about 15 Kg., 1 Gm. of cholesterol daily in their food, the cholesterol content of the blood was approximately doubled in one week; in one case it rose from 77 to 155 mg. per hundred cubic centimeters of bile and in the other case from 99 to 208 mg. At the time of operation, 24 cc. of hepatic bile (derived from another dog with a biliary fistula), containing 6.45 mg. of cholesterol, was introduced into the emptied gallbladder. At the end of twenty-four hours, 35.85 mg. of cholesterol was recovered from the contents of the gallbladder, an increase of 29.4 mg., or 455 per cent. From this it would seem that raising the concentration of the cholesterol in the blood increased the amount of cholesterol entering the gallbladder.

Dog VIII.—In this animal, instead of the cholesterol of the blood being raised, the cholesterol of the hepatic bile was raised by adding an excess of sterilized cholesterol to a flask containing sterile hepatic bile and shaking this every few hours for two days. Prior to the operation, the bile was carefully decanted and filtered through several layers of sterile gauze to prevent any particles of cholesterol from being present in the solution. This procedure raised the A bile cholesterol to 47.24 mg. per hundred cubic centimeters of bile. Thirty cubic centimeters

14. Lemoine and Gerard: Bull. et mém. Soc. méd. de hôp. de Paris **33**:931, 1912.

15. Rothschild, M. A., and Rosenthal, N.: Am. J. M. Sc. **152**:394, 1916.

of this bile, containing 14.17 mg. of cholesterol, was introduced into the gallbladder. At the end of tweny-four hours, 27.85 mg. of cholesterol was recovered, an increase of 12.68 mg., or 89.5 per cent. This result indicates that raising the cholesterol of the bile without raising that of the blood decreases the amount of cholesterol passing into the bile of the gallbladder.

The majority of animals used for these experimental purposes are not listed, owing to the fact that at the end of twenty-four hours the wall of the gallbladder in some instances was found to be inflamed or gangrenous in histologic sections; in others, the results were discarded owing to interference with the blood supply or to the presence of aberrant hepatic ducts emptying into the gallbladder above the ligature, occluding the cystic duct. Only the few animals in which no inflammatory changes were seen in the histologic sections of the gallbladder wall are listed in this article.

TABLE 1.—*Results in Experiments on Eight Dogs*

Dog	Dura-tion, Hours	Amount, Cc.		Mg. per 100 Cc. of Bile		Amount, Mg.		Change, Mg.	Percentage Change
		A	B*	A	B*	A	B		
I	24	10	3	35.85	182	3.58	5.46	1.88	52.0
II	24	31	12	22.75	239	7.05	28.69	21.64	307.0
III	24	29	14	19.61	105	5.69	14.76	9.07	159.0
IV	24	25	11	13.42	147	3.35	16.23	12.88	384.0
V	24	50	15	17.7	194	8.85	29.14	20.29	229.0
VI	38	25	10	20.05	312	5.01	31.26	26.25	524.0
VII	24	24	10	26.85	358	6.45	35.85	29.40	455.0
VIII	22	30	15	47.24	195	14.17	27.85	12.68	89.5

* Approximate.

Table 1 gives the main points in the foregoing experiments.

From table 1 it would appear that cholesterol passes into the bile of the gallbladder from without. It will also be noticed that the cholesterol concentration of B bile is only approximate, as it is difficult to measure the B bile accurately after concentration and precipitation has taken place. Nevertheless, it is interesting to note that the milligrams of cholesterol per hundred cubic centimeters in the B bile approximately corresponds to the average blood cholesterol content of the dog. The following four experiments bring this point out more clearly, as in these animals accurate readings of the cholesterol content of the blood were taken during the twenty-four hours that the experiment was taking place. It has been found that the cholesterol content of the blood of these dogs may vary greatly within short intervals, so it was necessary to check the blood at the beginning and the end of the period of concentration of the A bile.

In dogs IX and X no effort was made to raise the cholesterol content of the blood, but cholesterol was added to the bile.

It was found that the solubility of cholesterol in bile depends on the percentage of bile salts present; thus, by adding increasing percentages of sodium taurocholate and excess cholesterol to different portions of a sample of bile, the amount of cholesterol dissolved was raised proportionately to the percentage of bile salts:

	Cholesterol per 100 Cc. Bile
Bile + excess cholesterol	23.0 mg.
Bile + 1% sodium taurocholate + cholesterol	37.4 mg.
Bile + 2% sodium taurocholate + cholesterol	60.6 mg.
Bile + 10% sodium taurocholate + cholesterol	263.0 mg.

Dog IX.—Our procedure was to add sterile sodium taurocholate and cholesterol to sterile hepatic bile, until a high concentration of cholesterol dissolved in the bile was reached; the excess cholesterol was removed by filtration, and the concentration of cholesterol was found to be 184.9 mg. per hundred cubic centimeters of bile. The cystic duct was occluded as before, and 25 cc. of this A bile, containing 36.98 mg. of cholesterol, was introduced into the emptied gallbladder. At the end of twenty-four hours the animal was killed, and approximately 8 cc. of concentrated bile containing 12.5 mg. of cholesterol was removed from the gallbladder, indicating a loss of 24.48 mg. of cholesterol during the period of twenty-four hours. In other words, 8 cc. of B bile contained 12.5 mg. of cholesterol, corresponding to a concentration of approximately 156 mg. of cholesterol per hundred cubic centimeters of bile. The cholesterol of the blood throughout this experiment averaged 170.5 mg. per hundred cubic centimeters of blood, indicating that the loss of cholesterol from the gallbladder resulted in a final concentration of the cholesterol of the bile corresponding to that of the blood stream.

Dog X.—As in dog IX, A bile with an artificially high concentration was used. Twenty-five cubic centimeters containing 34.37 mg of cholesterol (or 137.5 mg per hundred cubic centimeters of bile) was injected. At the end of twenty-four hours, approximately 8 cc. of bile was recovered, which contained only 14.6 mg. of cholesterol (an approximate concentration of 182.5 mg. per hundred cubic centimeters of bile). The average cholesterol content of the blood throughout the experiment was 163.5 mg. per hundred cubic centimeters of blood. In this case there was a loss of 19.77 mg. of cholesterol from the gallbladder, resulting in a final cholesterol concentration of the bile approximately equal to that of the blood.

Dog XI.—This animal was fed 2 Gm. of cholesterol daily, which was mixed with its food. On the sixth day, at the time of operation, the cholesterol content of the blood was 366 mg. per hundred cubic centimeters of blood. At the end of twenty-four hours, it was 296 mg., giving an average cholesterol content of the blood during the period of bile concentration of 330 mg. After the cystic duct was ligated and

the gallbladder emptied, 25 cc. of hepatic bile derived from a biliary fistula of another dog, containing 8.32 mg. of cholesterol (or 33.3 mg. per hundred cubic centimeters of bile), was introduced into the gallbladder. After twenty-four hours, approximately 8 cc. of bile remained, which on analysis contained 25 mg. of cholesterol (or 312.5 mg. per hundred cubic centimeters of bile). The increase by weight of cholesterol at the end of twenty-four hours was 16.68 mg. The final concentration of cholesterol in the bile was approximately 312.5 mg. per hundred cubic centimeters, whereas the average concentration of cholesterol in the blood stream throughout the experimental period was 330 mg. per hundred cubic centimeters of blood. These figures suggest a close relationship between the two.

Dog XII.—The cholesterol content of the blood of this dog was raised to an average of 425 mg. by the measures that were employed in dog XI. Fourteen cubic centimeters of hepatic bile, containing 3.78 mg. of cholesterol (or 27 mg. per hundred cubic centimeters of bile),

TABLE 2.—*Results of Experiments on Dogs IX, X, XI and XII*

Dog	Dura-tion, Hours	Amount, Cc.		Mg. per 100 Cc. of Bile		Amount, Mg.		Change, Mg.	Percentage Change	Blood Cholesterol, Average
		A	B*	A	B*	A	B			
IX	24	25	8	184.9	136.0	36.98	12.5	−24.48	− 66.0	170.5
X	24	25	8	137.5	192.5	34.87	14.6	−19.77	− 57.5	168.5
XI	24	25	8	33.3	312.5	8.32	25.0	+16.68	+200.0	330.0
XII	24	14	8	27.0	430.0	3.78	12.9	+ 9.12	+241.0	425.0

* Approximate.

was introduced into the previously emptied gallbladder with the cystic duct occluded. At the end of twenty-four hours, approximately 3 cc. of bile was recovered, which contained 12.9 mg. of cholesterol (or 430 mg. per hundred cubic centimeters of bile). This shows an increase by weight in twenty-four hours of 9.12 mg. The cholesterol concentration of the bile was raised from 27 mg. to approximately 430 mg. per hundred cubic centimeters of bile, corresponding closely to the average cholesterol content of the blood of 425 mg. per hundred cubic centimeters of blood.

The results of the last four experiments are shown in table 2.

COMMENT

From the foregoing experiments it would appear that in normal dogs cholesterol passes into the bile of the gallbladder from without; that is, the cholesterol is derived in some way from the wall of the gallbladder and deposited in the bile. It would also seem logical to assume that the cholesterol is brought to the gallbladder by the blood stream.

It should be remembered that in this work the technic that was employed corresponds closely to the normal physiologic process. Normally, the gallbladder receives dilute hepatic bile. While in contact with the mucosa of the gallbladder, this bile is rapidly concentrated, principally by the removal of water. Changes in the other constituents of the bile that take place within the gallbladder most likely occur concomitantly with the absorption of the water.

The experimental method imitates closely the physiologic process so far as normal hepatic bile is placed in contact with the mucosa of the gallbladder, and concentration of this bile is allowed to proceed for twenty-four hours. In other words, under controlled quantitative conditions the normal process is reproduced, aside from the fact that the gallbladder is not continually receiving hepatic bile owing to the artificial occlusion of the cystic duct.

Before proceeding further, it should be mentioned that two minor inaccuracies are present in this work. First, when the bile is withdrawn from the gallbladder in the initial procedure, a small quantity of this bile is undoubtedly left in the gallbladder, which is not included in the determination of A bile. Second, when the gallbladder is removed to recover the B bile, a certain amount is also left adherent to the mucosa, which, of course, does not enter into the determination of cholesterol. The latter error is unavoidable, as any washing or scraping of the mucosa would be apt to remove some of the delicate membrane, and the cholesterol content of the cells would then be included in the calculations. It is, however, self-evident that these are but slight errors, and in any case the one tends to offset the other.

A careful analysis of the figures in table 1, aside from indicating that cholesterol normally passes from the blood stream into the bile through the wall of the gallbladder, brought up a further interesting observation. The question arose as to whether cholesterol enters the bile of the gallbladder by active secretion or merely by ordinary filtration. If cholesterol enters the gallbladder by filtration, this process should be dependent on the ratio between the cholesterol content of the blood and the bile, and it may be seen from the figures already given that the amount of cholesterol entering the gallbladder apparently does depend (to at least a great extent) on this ratio. In dog VII, which was fed a high cholesterol diet to produce hypercholesteremia, a large increase of cholesterol is found in the bile at the end of twenty-four hours. If, on the other hand, the cholesterol content of the bile is high and that of the blood normal, there is a much smaller interchange of cholesterol at the end of a given time. This fact is well demonstrated in dog VIII, in which cholesterol was artificially added to the A bile, resulting in a very small increase at the end of twenty-four hours.

Further, as Illingworth [4] and Boyd have shown, if very high concentrations of cholesterol are introduced into the gallbladder (that is, higher than the blood) it tends to disappear from the bile of the gallbladder.

Thus in dogs II, III, IV and V, with an average A bile of 18.37 mg. per hundred cubic centimeters of bile, the average increase of cholesterol was 269 per cent at the end of twenty-four hours. In dog VII, which was fed a high cholesterol diet, the increase was 455 per cent. In dog VIII, on the contrary, in which the cholesterol of the blood was probably normal and in which the cholesterol of the hepatic bile was artificially raised, the actual increase in twenty-four hours was only 89.5 per cent. It therefore seemed logical to assume the possibility that if the cholesterol concentration of the bile should be higher than that of the blood, cholesterol would pass from the bile into the blood stream.

With these facts in view, it was decided to perform a series of experiments in which the cholesterol content of the blood was carefully estimated along with that of the bile. As may be seen by table 2, observations were made on two animals (dogs IX and X) in which the cholesterol content of the bile was artificially raised, with that of the blood remaining within normal limits; on two other animals (dogs XI and XII), the cholesterol content of the bile was more or less normal, but that of the blood was definitely raised by feeding a high cholesterol diet. In studying table 2, it is interesting to note that the B bile, irrespective of the concentration of the A bile, tends to approach an equilibrium with the cholesterol content of the blood. Two factors are involved in the production of this apparent equilibrium: (1) the reduction in volume of the A bile by the absorption of fluid; (2) the interchange of cholesterol between the bile and the blood stream, one way or another.

Dog XII, in which there was marked concentration, is a good example of both these points, the bile being concentrated from 14 to 3 cc. in twenty-four hours by the absorption of fluid. The 14 cc. of bile injected contained 3.78 mg. of cholesterol. If this amount of cholesterol remained constant and reduction in volume by removal of water were the only factor, the final 3 cc. of bile would have a cholesterol concentration of 127 mg. per hundred cubic centimeters of bile. Actually the final cholesterol concentration of the B bile was 430 mg. per hundred cubic centimeters of bile, which corresponds closely to that of the blood (425 mg. per hundred cubic centimeters of blood). We may therefore assume that this result was attained by the passage of cholesterol from the blood stream into the bile. In other words, although the absolute increase by weight of cholesterol in twenty-four hours was small (9.12 mg.), the combined effect of reduction in volume and of addition of cholesterol was to raise the cholesterol concentration of the B bile to a level with that of the blood.

In dogs IX and X, the equilibrium of cholesterol concentration between the blood and the bile was attained by the loss of cholesterol from the bile, compensating for the increased concentration due to the loss of fluid. Thus in dog IX the A bile concentration was 184.9 mg. per hundred cubic centimeters of bile (25 cc. containing 36.98 mg.), slightly higher than that of the blood (170.5 mg. per hundred cubic centimeters of blood). As before, if concentration were the only factor involved, the final 8 cc. of bile would show a concentration of 462.25 mg. of cholesterol per hundred cubic centimeters of bile. Actually, the final cholesterol concentration was only 156 mg. per hundred cubic centimeters of bile, approximating that of the blood. This result could be attained only by a loss of cholesterol from the bile of the gallbladder.

CONCLUSIONS

1. In normal animals, with the cystic duct tied, when the cholesterol concentration of the bile is lower than that of the blood, cholesterol passes from the blood through the mucosa of the gallbladder into the bile.

2. When the cholesterol concentration of the bile is higher than that of the blood, cholesterol passes from the bile through the mucosa of the gallbladder into the blood stream.

3. The amount of cholesterol passing through the mucosa and the direction of its passage apparently depend on the blood-bile cholesterol ratio.

EFFECTS ON COMPOSITION OF BLOOD OF PHYSIO-LOGIC SOLUTION OF SODIUM CHLORIDE

WHEN INTRODUCED BY INTRAPERITONEAL INJECTION AND BY STOMACH TUBE IN THE PRESENCE OF LOW BLOOD PRESSURE

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This paper is a continuation of previously reported studies [1] of the effects of the administration of fluids to animals with low blood pressure. In the previous studies, fluid was administered intravenously and subcutaneously. The changes observed in the protein content of the blood were considered important. The present studies were carried out in order to determine the effects of physiologic solution of sodium chloride when introduced by intraperitoneal injection and by stomach tube into animals with low blood pressure. The subcutaneous injection of histamine and graded bleeding were the methods used to produce low blood pressure.

METHODS

All of the experiments were carried out on dogs that were anesthetized with morphine. They gave no evidence of pain during the experiments. Shortly following the administration of the anesthetic, the blood volume was determined by

the dye method,[2] and samples of blood were withdrawn for the control determinations. Physiologic solution of sodium chloride was then introduced intraperitoneally or by stomach tube. When introduced into the peritoneal cavity, it was injected through a needle at a constant rate of 10 cc. per kilogram of body weight per hour for four hours. Samples of blood were removed for the analyses one, two and one-half and four hours following the beginning of the injection of fluid, and one and one-half and three hours following its completion. When given by stomach tube, one half of the amount, equal to 10 cc. per kilogram of body weight per hour for four hours, was given at the beginning of the experiment, and the remainder at the end of two hours. At the completion of the experiment, the amount of fluid remaining in the stomach or peritoneal cavity was measured. Following the withdrawal of a sample of blood, it was replaced by an equal amount obtained from another dog.

Experiments were first performed in which the effects of administration of fluids to normal dogs by the methods described were determined. In subsequent experiments the blood pressure was caused to decline by the withdrawal of blood from the femoral vein at intervals at the rate of 10 cc. per kilogram of body weight per hour for four hours. In the experiments in which the decline in pressure was produced by histamine, a solution of 0.1 per cent histamine phosphate was injected in sufficient amounts to maintain a depression of the blood pressure.

The hemoglobin was determined by the method described by Cohen and Smith.[3] Van Allen tubes were used for the hematocrit readings. The blood for protein analyses was allowed to clot, and the determinations were carried out on blood serum. The proteins were partitioned by the use of 22.2 per cent sodium sulphate, as recommended by Howe,[4] and the total protein content, the albumin content and the globulin content of each sample were determined by the Macro-Kjeldahl method, according to Gunning's modification.[5] On the basis of the original blood volume determined directly by the dye method, changes in blood volume were calculated from alterations in the hemoglobin. From the hematocrit estimations, the relative volumes of red blood cells and of plasma could be calculated. The absolute amount of protein in the circulation was calculated from protein per unit volume and plasma volume.

RESULTS

I. *Effects on the Composition of the Blood of Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity.* —*A.* When the Blood Pressure Remained at a Normal Level: Three experiments were carried out, the results of which were entirely similar. There was a definite increase in plasma volume in each experiment, and a slight decrease in the amount of protein per unit volume. There was a small increase in the calculated absolute amount of protein in the entire

2. Rowntree, L. G., and Brown, G. E.: The Volume of the Blood and Plasma in Health and Disease, Mayo Clinic Monographs, Philadelphia, W. B. Saunders Company, 1929.

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circulation. The changes in albumin and globulin were parallel to those in the total protein. In the three experiments, the average amount of fluid absorbed from the peritoneal cavity was 34 per cent of that injected. The results of these experiments are shown in table 1.

B. When the Blood Pressure Is Lowered by the Subcutaneous Administration of Histamine: The results of these experiments, of which there were three, differ considerably from those of the controls. There was a diminution in the amount of blood plasma in the circulation in all experiments. The percentage of protein per unit volume of plasma changed little. There was definite diminution in the absolute amount of plasma protein. The results of these experiments are given in table 2.

C. When the Blood Pressure Is Lowered by Hemorrhage: Two experiments were performed. The results obtained were essentially the same in each. The diminution of plasma volume was less than the amount present in the blood that was removed. There was a slight decrease in the percentage of protein. The absolute amount of protein in the circulation decreased, but if correction is made for the amount of protein removed in the blood a slight gain was shown. These figures are placed in brackets in the tables. An average of 24 per cent of the fluid placed in the peritoneal cavity during the two experiments was absorbed. The results of these experiments are shown in table 3.

II. *Effects on the Composition of the Blood of Introduction of Physiologic Solution of Sodium Chloride into the Stomach.—A*. When the Blood Pressure Remains at a Normal Level: The administration of physiologic solution of sodium chloride by stomach tube to dogs the blood pressure of which remained at essentially the normal level throughout the experiment caused little alteration in the percentage of protein of the blood serum. The results of one of the three experiments showed considerable loss of plasma during the experiment and a comparable loss of total protein. There was a slight increase in plasma volume in one experiment and a very slight diminution in the other. In the former, the absolute amount of protein in the circulation at the end of the experiment was almost exactly the same as at the control period, while in the latter, 2 Gm. of protein was lost during the seven hours. The results of these experiments are shown in table 4.

B. When the Blood Pressure Is Caused to Decline by the Subcutaneous Administration of Histamine: In both experiments of this series there was definite and considerable diminution in the plasma volume and comparable loss of protein. The protein per unit volume remained constant, and these results are essentially identical with those obtained when histamine is injected and no fluid is administered. Almost as much fluid

TABLE 1.—Effects on the Composition of the Blood of the Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity

Experiment	Time from Beginning	Amount of Fluid Given	Total Protein		Albumin		Globulin		Blood Volume from Hemoglobin and Hematocrit			Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
			Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Red Blood Cells	Plasma	Whole			
T 161 10.8 Kg.	Control	0	7.2	65.4	3.00	27.8	4.20	37.6	(337)	(928)	(1,565)	40.7	87.7	122
	1 hr.	168	7.2	67.2	3.08	29.4	4.12	37.8	637	955	1,592	40.0	86.2	105
	2 hr. 30 min.	386	7.2	66.8	3.00	28.5	4.20	38.3	646	949	1,595	40.5	86.0	122
	4 hr.	672	6.61	62.6	2.91	27.7	3.70	34.9	633	942	1,575	40.2	87.2	109
	5 hr. 30 min.	...	6.51	67.8	3.05	31.6	3.40	36.2	615	1,035	1,675	38.2	82.0	108
	7 hr.	...	6.57	67.0	2.83	28.9	3.74	38.1	645	1,020	1,665	38.8	82.4	101
	Injected blood	...	8.38	...	3.22	...	5.16	...	...	...	...	33.5	63.0	...
T 165 17.31 Kg.	Control	0	5.91	58.0	3.31	32.7	2.57	25.3	(545)	(980)	(1,825)	35.7	77.3	118
	1 hr.	173	5.78	56.8	3.25	32.0	2.53	24.8	532	983	1,616	35.2	77.7	111
	2 hr. 30 min.	398	5.51	57.2	3.00	30.0	2.51	26.3	535	1,030	1,565	31.1	75.4	105
	4 hr.	682	5.69	58.9	3.11	32.0	2.58	26.9	535	1,015	1,570	31.2	75.0	111
	5 hr. 30 min.	...	5.59	59.0	3.03	31.9	2.56	27.1	530	1,055	1,585	33.4	74.3	104
	7 hr.	...	5.50	60.2	2.91	32.2	2.56	28.0	521	1,091	1,615	32.3	73.0	101
	Injected blood	...	7.05	...	2.43	...	4.62	...	...	...	...	29.0	61.1	...
T 166 13.65 Kg.	Control	0	6.25	55.6	...	32.6	...	...	(505)	(570)	(1,075)	47.0	103.4	153
	1 hr.	130	6.19	56.9	3.99	33.8	2.20	23.1	516	596	1,112	40.4	100.0	132
	2 hr. 30 min.	310	6.05	55.7	3.85	32.7	2.20	23.0	522	590	1,112	40.0	100.0	145
	4 hr.	541	6.05	57.5	3.85	33.7	2.20	23.8	531	610	1,160	46.2	96.5	145
	5 hr. 30 min.	...	5.91	56.7	...	...	...	...	519	621	1,160	46.0	96.5	135
	7 hr.	...	5.82	58.3	3.56	33.5	2.26	24.8	542	658	1,200	45.2	92.6	125
	Injected blood	...	7.57	...	3.59	...	3.78	...	...	...	...	36.9	62.5	...

Protocols.—T 161: A total of 672 cc. of fluid was injected at the rate of 10 cc. per kilogram per hour into the peritoneal cavity. All the end of the experiment 475 cc. was recovered from the cavity, leaving 197 cc. that had been absorbed.

T 165: Fluid was injected into the peritoneal cavity continuously at the rate of 10 cc. per kilogram per hour, and a total of 682 cc. was injected. At the end of the experiment 370 cc. was recovered, and 322 cc. had been absorbed.

T 166: Fluid was injected into the peritoneal cavity continuously at the rate of 10 cc. per kilogram per hour, and a total of 541 cc. was injected. At the end of the experiment 415 cc. was recovered, and 120 cc. had been absorbed.

TABLE 2.—*Effects of the Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity in the Presence of a Decline in Blood Pressure Produced by the Subcutaneous Injection of Histamine*

Experiment	Time from Beginning	Amount of Fluid Given	Histamine, Mg.	Total Protein Blood, per cent Hemoglobin Hematocrit	Total Protein Entire from Hemoglobin and Hematocrit	Albumin Blood, per cent Hemoglobin Hematocrit	Albumin Entire from Hemoglobin and Hematocrit	Globulin Blood, per cent Hemoglobin Hematocrit	Globulin Entire from Hemoglobin and Hematocrit	Blood Volume Red Blood Cells	Blood Volume Plasma	Blood Volume Whole	Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
T 159 9.5 Kg.	Control	0	10	5.30	28.2	2.83	15.0	2.47	13.2	(302)	(632)	(834)	36.2	82.1	108
	1 hr.	95	25	5.78	29.7	3.14	16.1	2.64	13.4	311	514	825	37.8	83.3	82
	2 hr. 30 min.	238	40	5.78	29.5	3.03	15.5	2.75	14.0	315	510	825	38.2	83.3	65
	4 hr.	380	...	5.60	27.5	2.72	13.4	2.88	14.1	323	492	815	39.7	81.3	57
	5 hr. 30 min.	...	...	5.55	27.5	2.66	13.2	2.89	14.3	317	495	812	38.0	84.7	57
	7 hr.	...	...	4.88	24.8	2.43	12.4	2.45	12.4	317	508	825	38.1	83.3	74
	Injected blood	...	...	7.40	....	2.32	....	5.18	....	...	...	...	29.7	65.3	...
T 160 12 Kg.	Control	0	10	4.71	33.0	2.49	17.1	2.22	15.6	(503)	(700)	(1,203)	41.8	70.9	100
	1 hr.	120	15	5.05	28.7	2.23	12.7	2.82	16.0	512	...	1,080	47.1	101.3	63
	2 hr. 30 min.	300	20	5.46	25.5	2.43	11.4	3.03	14.5	509	467	976	52.2	111.9	67
	4 hr.	480	...	5.55	23.4	2.32	9.78	3.23	13.6	550	422	952	55.6	115.4	93
	5 hr. 30 min.	...	...	5.08	23.3	2.60	10.7	2.08	12.7	525	411	930	56.0	117.1	116
	7 hr.	...	...	5.08	25.2	2.55	11.3	3.13	13.9	526	411	...	54.2	112.7	100
	Injected blood	...	...	6.23	....	3.66	....	3.17	....	...	...	...	41.5	89.3	...
T 161 10 Kg.	Control	0	10	6.23	36.0	3.62	20.9	2.61	15.8	(390)	(578)	(968)	40.1	92.0	120
	1 hr.	100	15	6.31	31.2	3.70	18.1	2.61	12.9	419	495	911	45.0	97.4	97
	2 hr. 30 min.	250	20	6.31	29.3	...	...	...	...	405	465	870	46.2	101.3	81
	4 hr.	400	45	6.50	28.2	3.90	16.0	2.60	11.3	408	431	812	48.5	105.6	65
	5 hr. 30 min.	...	...	6.23	24.9	2.79	15.2	3.54	9.7	420	400	820	51.2	108.7	113
	7 hr.	...	...	5.87	24.2	3.42	11.1	2.45	10.1	420	412	832	50.5	107.1	101
	Injected blood	...	...	4.37	....	2.49	....	1.88	....	...	...	...	33.4	75.0	...

Protocols.—T 159: Following the control determination 10 mg. of histamine was administered subcutaneously, and the injection of fluid into the peritoneal cavity was begun at the same time. The total amount of fluid given was 380 cc., and at the end of the experiment 170 cc. was recovered from the peritoneum. The amount absorbed was, therefore, 210 cc. A total of 40 mg. of histamine was administered during the experiment.

T 160: Following the control determination 10 mg. of histamine was administered subcutaneously, and the injection of fluid into the peritoneal cavity was begun at the same time. The total amount of fluid given was 480 cc., and at the end of the experiment 525 cc. was recovered. Not only was no fluid absorbed, but there was a transudation of 45 cc. into the peritoneum. A total of 20 mg. of histamine was administered during the experiment.

T 161: Following the control determination 10 mg. of histamine was administered subcutaneously, and the injection of fluid into the peritoneal cavity was begun at the same time. The total amount of fluid given was 400 cc., and at the end of the experiment 205 cc. was recovered. The amount absorbed was, therefore, 205 cc. A total of 45 mg. of histamine was administered during the experiment.

TABLE 3.—*Effects of the Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity in the Presence of a Decline in Blood Pressure Produced by Graded Hemorrhage*

Experiment	Time from Beginning	Amount of Fluid Given	Amount of Blood Withdrawn	Total Protein Blood, per Cent Hematocrit	Total Protein Entire from Hemoglobin and Hematocrit	Albumin Blood, per Cent Hematocrit	Albumin Entire from Hemoglobin and Hematocrit	Globulin Blood, per Cent Hematocrit	Globulin Entire from Hemoglobin and Hematocrit	Blood Volume Red Blood Cells	Blood Volume Plasma	Blood Volume Whole	Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
T 157 16.58 Kg.	Control	0	166	7.14	(93.5)/85.2	2.83	(34.1)/31.1	4.31	(59.1)/51.1	(555)	(1,295)	(1,850)	30.0	69.4	107
	1 hr.	160	414	7.01	(93.2)/85.2	2.57	(36.6)/28.0	4.47	(61.5)/48.7	500	1,210	1,710	29.1	68.2	95
	2 hr. 30 min.	415	662	6.73	(98.2)/77.0	2.51	(36.6)/28.9	4.22	(62.7)/48.2	441	1,151	1,595	27.7	62.5	103
	4 hr.	611	…	6.45	(102.6)/70.0	2.51	(39.5)/27.2	3.01	(62.7)/42.8	370	1,085	1,455	25.3	57.9	76
	5 hr. 30 min.	…	…	6.32	(101.2)/68.0	2.38	(38.1)/25.8	3.01	(67.7)/42.8	370	1,085	1,455	25.1	57.9	61
	7 hr.	…	…	6.11	(88.2)/55.0	2.43	(33.4)/21.1	3.08	(55.4)/31.5	377	858	1,235	30.6	68.2	66
T 158 13.5 Kg.	Control	0	135	6.70	46.0	4.02	27.7	2.68	18.3	(452)	(988)	(1,140)	39.6	88.2	132
	1 hr.	135	337	6.41	(43.6)/38.1	3.88	(26.3)/23.0	2.53	(17.2)/15.1	411	591	1,005	40.9	88.2	114
	2 hr. 30 min.	338	510	6.14	(45.0)/32.8	3.39	(26.0)/18.1	2.75	(19.8)/14.7	390	534	864	38.2	82.0	125
	4 hr.	510	…	5.97	(47.3)/26.5	3.42	(27.3)/15.2	2.55	(19.8)/11.3	243	414	657	35.4	79.0	80
	5 hr. 30 min.	…	…	5.73	(47.2)/24.1	3.42	(29.0)/16.8	2.31	(19.1)/10.6	256	460	716	35.3	75.8	61
	7 hr.	…	…	5.61	(47.5)/26.7	3.25	(27.5)/15.4	2.39	(19.8)/11.3	243	473	716	31.0	76.8	51

Protocols.—T 157: Following the control determination 106 cc. of blood was withdrawn; at the end of two and a half hours another 218 cc. was withdrawn. An equivalent amount of fluid was injected continuously at the rate of 10 cc. per kilogram per hour, beginning simultaneously with the initial withdrawal of blood. A total of 611 cc. of fluid was given, and at the end of the experiment 420 cc. was recovered. The amount of fluid absorbed was 224 cc.

T 158: Following the control determination 135 cc. of blood was withdrawn; at the end of one hour 202 cc. was withdrawn, and at the end of two and a half hours another 218 cc. was withdrawn. An equivalent amount of fluid was injected continuously into the peritoneal cavity at the rate of 10 cc. per kilogram per hour beginning simultaneously with the initial withdrawal of blood. A total of 510 cc. of fluid was given, and at the end of the experiment 297 cc. was recovered. The amount of fluid absorbed was 213 cc.

TABLE 4.—*Effects on the Composition of the Blood of Introduction of Physiologic Solution of Sodium Chloride into the Stomach*

Experiment	Time from Beginning	Amount of Fluid Given	Total Protein		Albumin		Globulin		Blood Volume from Hemoglobin and Hematocrit			Hemato-crit	Hemo-globin	Mean Blood Pressure, Mm. Hg
			Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Red Blood Cells	Plasma	Whole			
T 162 10.75 Kg.	Control	0	6.47	57.4	2.89	25.6	3.58	31.8	(573)	(887)	(1,460)	39.3	88.2	133
	1 hr.	167	6.64	55.1	3.11	25.8	3.53	29.3	595	830	1,425	41.7	90.5	117
	2 hr. 30 min.	412	6.82	58.0	3.23	27.4	3.59	30.6	590	850	1,440	41.1	89.3	135
	4 hr.	608	6.55	52.4	3.31	26.5	3.24	25.9	570	800	1,370	41.6	93.8	135
	5 hr. 30 min.	...	6.47	59.5	3.06	28.1	3.41	31.4	595	920	1,515	40.3	85.2	108
	7 hr.	...	6.28	57.7	2.72	24.0	3.56	32.3	621	918	1,539	40.0	81.3	117
	Injected blood		0.64	...	2.21	...	4.43	...	...	...	.....	29.3	66.3	...
T 163 10.15 Kg.	Control	0	6.50	60.2	...	...	...	...	(640)	(1,065)	(1,705)	37.5	79.0	145
	1 hr.	101	5.82	53.1	...	...	...	...	613	912	1,520	40.3	88.2	125
	2 hr. 30 min.	478	6.09	54.6	...	...	...	...	649	896	1,545	42.0	87.2	130
	4 hr.	764	5.87	53.4	...	...	...	...	650	910	1,560	41.8	80.2	144
	5 hr. 30 min.	...	5.87	49.2	...	...	...	...	642	893	1,480	43.5	90.0	140
	7 hr.	...	6.12	47.1	...	...	...	...	650	770	1,420	45.8	94.9	135
	Injected blood		5.41	...	...	...	...	...	...	...	.....	21.8	50.0	...
T 164 12.0 Kg.	Control	0	6.17	38.8	3.85	24.1	2.32	14.7	(497)	(628)	(1,125)	44.2	95.5	132
	1 hr.	129	6.22	37.2	3.63	21.5	2.67	15.7	495	588	1,083	45.7	99.3	137
	2 hr. 30 min.	323	6.43	37.0	3.62	20.7	2.81	16.3	503	572	1,075	40.8	100.0	133
	4 hr.	516	6.28	34.7	3.77	20.8	2.51	13.9	503	552	1,060	47.9	99.3	126
	5 hr. 30 min.	...	6.37	35.3	3.60	20.0	2.77	15.3	505	555	1,060	47.7	101.3	106
	7 hr.	...	6.10	30.3	3.39	20.2	2.71	16.1	501	595	1,090	45.7	98.0	102
	Injected blood		7.1	...	3.14	...	3.96	...	...	...	.....	32.0	79.0	...

Protocols.—T 162: Fluid was run into the stomach continuously through a stomach tube, at the rate of 10 cc. per kilogram per hour. A total of 688 cc. was given. At the end of the experiment 110 cc. was found in the stomach. The dog vomited 70 cc. at the end of the second hour.

T 163: A total of 764 cc. of fluid was placed in the stomach during the experiment; one-half was run in at the beginning, and the other half was run in at the end of two hours. At the end of the experiment 385 cc. of fluid remained in the stomach and 110 cc. was found in the peritoneal cavity. The dog did not vomit.

T 164: A total of 510 cc. of fluid was placed in the stomach during the experiment; one-half was run in at the beginning, and the other half at the end of two hours. At the end of the experiment 35 cc. of fluid remained in the stomach. The dog did not vomit.

Table 5.—*Effects of Introduction of Physiologic Solution of Sodium Chloride into the Stomach in the Presence of a Decline in Blood Pressure Produced by the Subcutaneous Injection of Histamine*

Experiment	Time from Beginning	Amount of Fluid Given	Histamine, Mg.	Total Protein — Blood, per Cent	Total Protein — Entire from Hemoglobin and Hematocrit	Albumin — Blood, per Cent	Albumin — Entire from Hemoglobin and Hematocrit	Globulin — Blood, per Cent	Globulin — Entire from Hemoglobin and Hematocrit	Blood Volume from Hemoglobin and Hematocrit — Red Blood Cells	Plasma	Whole	Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
T 167, 15.0 Kg.	Control	0	0	7.52	61.1	4.21	35.2	3.11	26.2	(675)	(838)	(1,513)	44.7	102.7	135
	1 hr.	156	30	7.37	47.5	4.16	27.8	3.21	20.7	722	644	1,366	52.9	113.6	98
	2 hr. 30 min.	390	65	7.63	41.5	4.21	24.6	3.42	10.0	742	581	1,323	56.0	117.1	85
	4 hr.	621	125	7.10	42.9	4.01	21.1	3.15	18.8	753	597	1,350	55.8	115.4	81
	5 hr. 30 min.	: :	: :	7.60	41.8	4.33	24.7	3.27	20.1	793	597	1,390	57.0	111.9	115
	7 hr.	: :	: :	7.70	40.0	4.8	25.0	2.99	21.0	792	598	1,390	56.0	111.9	102
	Injected blood	....		6.46	....	1.07	....	5.40	....	....	....	....	33.1	79.0	....
T 168, 17.7 Kg.	Control	0	0	6.11	41.0	4.75	31.1	1.38	9.0	(573)	(717)	(1,290)	41.5	91.0	110
	1 hr.	177	60	6.21	31.7	4.97	27.0	1.27	7.1	561	550	1,120	50.3	101.0	90
	2 hr. 30 min.	113	80	5.92	35.9	4.52	27.4	1.40	8.5	551	606	1,160	47.8	101.3	65
	4 hr.	698	120	6.06	30.1	4.52	26.9	1.44	0.2	564	596	1,160	48.6	101.3	83
	5 hr. 30 mm.	: :	: :	6.28	31.2	4.66	25.3	1.62	8.9	551	544	1,095	50.3	107.1	103
	7 hr.	: :	: :	6.14	32.3	4.50	23.7	1.61	9.6	569	526	1,095	52.0	107.1	101
	Injected blood	....		6.96	....	2.83	....	4.13	....	....	....	....	29.0	62.5	....

Protocols. T 167: A total of 621 cc. of fluid was placed in the stomach, one-half at the beginning of the experiment and the other half two hours later. Following the control determinations 10 mg. of histamine was administered, and enough thereafter to keep the blood pressure depressed. At the end of the experiment 550 cc. of fluid was found in the stomach. There was no vomiting.

T 168: A total of 700 cc. of fluid was placed in the stomach, one-half at the beginning of the experiment and the other half two hours later. Following the control determinations 10 mg. of histamine was administered, and enough thereafter to keep the blood pressure depressed. At the end of the experiment 550 cc. of fluid was found in the stomach. There was no vomiting.

TABLE 6.—*Effects of Introduction of Physiologic Solution of Sodium Chloride into the Stomach in the Presence of a Decline in Blood Pressure Produced by Graded Hemorrhage*

Experiment	Time from Beginning	Amount of Fluid Given	Amount of Blood Withdrawn	Total Protein Blood, per Cent	Total Protein Entire from Hemoglobin and Hematocrit	Albumin Blood, per Cent	Albumin Entire from Hemoglobin and Hematocrit	Globulin Blood, per Cent	Globulin Entire from Hemoglobin and Hematocrit	Blood Volume from Hemoglobin and Hematocrit Red Blood Cells	Plasma	Whole	Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
T 165 12.7 Kg.	Control	0	127	5.91	46.1 (48.9)	3.70	23.8 (30.1)	2.21	17.3 (18.7)	(456)	(780)	(1,236)	36.9	79.0	115
	1 hr.	127	317	5.54	44.2 (49.2)	3.42	27.3 (30.1)	2.12	16.9 (18.4)	392	798	1,190	32.6	73.5	98
	2 hr. 30 min.	318	417	5.58	36.9 (49.4)	3.48	23.0 (29.5)	2.00	13.9 (19.1)	350	660	1,010	31.6	72.8	88
	4 hr.	508	...	5.80	33.3 (39.8)	3.50	20.1 (29.7)	2.30	13.2 (19.3)	309	571	883	35.0	75.0	62
	6 hr. 15 min.	...	...	6.09	33.7	3.37	20.3	2.22	13.4	311	603	911	31.0	72.5	39
T 166 12.1 Kg.	Control	0	121	7.14	42.7 (43.4)	4.67	28.0 (26.3)	2.47	14.7 (17.1)	(539)	(599)	(1,138)	47.1	103.6	132
	1 hr.	121	276	7.68	38.0 (43.0)	4.61	23.3 (26.6)	3.07	15.7 (17.3)	490	506	1,002	49.5	107.1	133
	2 hr. 30 min.	303	...	7.56	33.4 (42.4)	4.53	20.0 (25.9)	3.03	13.4 (16.5)	417	442	859	48.5	103.6	70
	4 hr.	481	...	7.41	31.9	4.50	19.3	2.91	12.6	417	430	817	49.2	107.1	76

Protocols.—T 165: A total of 508 cc. of fluid was given into the stomach, 251 cc. at the beginning of the experiment and 251 cc. at the end of the second hour. Blood was withdrawn at intervals to equal 10 cc. per kilogram per hour. The third bleeding in the experiment was of 100 cc. which produced such a profound fall in pressure that the full amount could not be taken. Blood pressure declined gradually from this point, and the animal died at the end of five hours and forty-five minutes. The amount of fluid found in the stomach was 525 cc., while only 508 cc. had been injected.

T 166: In this experiment, the animal tolerated only two hemorrhages, 121 cc. at the beginning of the experiment and 155 cc. at the end of the second hour and a half. This dog died in four and a half hours. The total fluid placed in the stomach was 484 cc., and 425 cc. was recovered at the end of the experiment.

was found in the stomach of these dogs at the end of the experiment as was placed in them during the experimental period. The results of these experiments are given in table 5.

C. When the Blood Pressure Is Caused to Decline as the Result of Hemorrhage: It is perhaps significant that the animals in these two experiments neither tolerated the withdrawal of 10 cc. of blood per kilogram per hour for four hours nor lived through the usual seven hours of the experiments. The absolute amount of plasma protein in the circulation decreased, but this loss was accounted for by the protein in the withdrawn blood. The percentage of protein per unit volume of· serum remained practically constant. The volume of blood plasma decreased rather markedly. Almost all of the fluid placed in the stomachs of these dogs was recovered at the end of the experiments. The results of these experiments are shown in table 6.

COMMENT

The usual methods by which fluids are administered are intravenously, subcutaneously, intraperitoneally, by mouth and by rectum. In previous studies,[1] the effects on the composition of the blood of the administration of various fluids intravenously and of physiologic solution of sodium chloride subcutaneously to animals with a normal blood pressure and to those in which a decline in blood pressure had been produced by several means were determined. Particular emphasis has been placed on alterations in the percentage and absolute amounts of plasma protein, because protein maintains to a large degree the osmotic pressure of the blood stream. It has been shown previously [6] that the fluid that escapes from the blood stream as a result of trauma to the intestines, mild trauma to an extremity and burns has approximately the same protein content as the plasma of the blood stream. The introduction of physiologic solution of sodium chloride intravenously and of most of the other solutions frequently used in the treatment of shock caused little alteration in the composition of the blood when injected into dogs with normal blood pressures. When a decline in blood pressure was produced by hemorrhage and fluids were injected intravenously, the loss of protein was limited to that removed in the withdrawn blood. On the contrary, the intravenous injection of fluid into animals in which gross capillary injury had been inflicted by either mechanical or chemical means resulted in a loss of most of the fluid that was injected and in addition, in a decrease in the percentage of protein in the plasma remaining in the blood vessels. When salt solution was injected subcutaneously

6. Beard, J. W., and Blalock, A.: Experimental Shock. VIII. The Composition of the Fluid that Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines and After Burns, Arch. Surg. **22**:617 (April) 1931.

into normal animals, there was little alteration in the composition of the blood. The subcutaneous injection of physiologic solution of sodium chloride into animals from which blood was removed was not associated with any additional loss of protein. In some instances there was a slight increase in the absolute amount of plasma protein if correction is made for the amount removed. When the subcutaneous injection of salt solution was accompanied by injury to large areas of capillaries, there was a large loss of protein from the circulation but that remaining was not diluted greatly, as was found in the experiments in which the fluid was given intravenously.

The results of the present experiments in which physiologic solution of sodium chloride was injected into the peritoneal cavity are similar to those that were obtained in the studies in which the fluid was injected subcutaneously. If any difference is present, it is in favor of the more rapid absorption by the blood stream of the fluid that was placed in the peritoneal cavity.

When, however, the salt solution was placed in the stomach, the results were similar to those obtained when no fluid was administered by any route. Studies of the composition of the blood indicated little if any absorption of the fluid that was placed in the stomach. It is possible that the morphine that was used as the anesthetic might have diminished the absorption of the fluid.

SUMMARY

The effects on the composition of the blood of the introduction of physiologic solution of sodium chloride intraperitoneally and by stomach tube into normal dogs and into dogs in which a decline in blood pressure was produced by hemorrhage and by histamine have been determined. The studies included determinations of the arterial blood pressure, the percentage of hemoglobin, the concentration of the red blood cells, the volumes of whole blood, red blood cells and plasma, and the percentages of total protein, albumin and globulin in the blood serum.

The introduction of physiologic solution of sodium chloride into the peritoneal cavity of the normal dog was associated with an increase in the volume of plasma, a slight dilution of the protein of the plasma and a small increase in the absolute amount of plasma protein. When the blood pressure was caused to decline by giving histamine subcutaneously and salt solution was injected into the peritoneal cavity, there was a diminution in the volume of plasma and in the absolute amount of plasma protein. The percentage of protein per unit volume of plasma changed very little. The removal of blood and the introduction of salt solution intraperitoneally were associated with decreases in the plasma volume and in the absolute amount of plasma protein. However, the

losses of protein and plasma were less than the amounts removed in the blood. There was a slight dilution of the protein remaining in the circulation. The findings in these experiments in which the fluid was introduced intraperitoneally were similar to those obtained following the subcutaneous injection of solution.

The experiments in which physiologic solution of sodium chloride was introduced by stomach tube into normal dogs and into dogs with a low blood pressure showed no appreciable effects of the administration of fluid.

ABSORPTION OF DEXTROSE FROM THE COLON

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The ease with which fluids can be introduced through the rectum into the colon has resulted in the widespread use of this method for the administration of a variety of substances. There is undoubtedly a paucity of evidence from carefully controlled experiments on the ability of the colonic mucous membrane to absorb protein, fat or carbohydrate. It is well known that the rectal administration of ether results in general anesthesia. More recently the success with which narcosis may be produced by the rectal administration of sodium amytal and avertin proves that fairly complicated molecules may be absorbed by the mucosa of the large bowel. The sedative effect produced by the colonic administration of chloral hydrate or sodium bromide is a well established clinical phenomenon. The bromide ion, when administered rectally in sufficient amounts, can be recovered from the urine, the sweat and the lacrimal secretions. Recently, Cohn,[1] in this laboratory, found that iodine is readily absorbed from the colon.

The nutritive substance most often given either by rectal drip or by massive colonic instillation is dextrose. It supplies a variety of needs in the body economy. The evidence of its utilization when given into the large bowel has until recently been rather meager. Every textbook of therapeutics stresses the efficacy of administering dextrose by rectum to those patients requiring carbohydrates in instances in which the oral route cannot be used. No chapter on diabetes misses the opportunity of mentioning that dextrose may be administered by proctoclysis when necessary. In most surgical clinics the method has been used whenever the use of dextrose has been indicated and its administration by any other route has been inadvisable. The evidence on the total caloric value of the dextrose that can be absorbed from the large bowel is quite indefinite.

1. Cohn, B. N. E.: The Absorption of Compound Solution of Iodine from the Gastro-Intestinal Tract with Special Reference to Absorption of Free Iodine, Arch. Int. Med. **49**:950 (June) 1932.

Recently, experimental data published by McNealy and Willems [2] and by Scott and Zweighaft [3] question the ability of the large bowel to absorb dextrose. The experiments of McNealy and Willems were carried out on the colon of the dog. The large rectal ampulla was not utilized. Because of this, similar experiments have been performed, the entire colon and rectum being used—a method employed by Goldschmidt and Dayton [4] in their sodium chloride experiments. These studies have been extended to include a study of the degree to which the pancreatectomized dog with hyperglycemia and the hypoglycemic animal will absorb dextrose from the same portion of the alimentary tract. It is hoped that the present experiments will enhance our knowledge of the advisability and efficacy of administering dextrose by the rectal route as a therapeutic measure in the diabetic and nondiabetic patient. The step from the laboratory animal to the human patient is not so great but that some comparisons can be drawn.

REVIEW OF THE LITERATURE

The early literature is replete with a variety of mixtures which were supposedly efficacious in maintaining life when given by the rectal route. How trustworthy these reports are cannot be stated.

Voit and Bauer [5] performed the first systematic research on the absorptive mechanism of the colon. Their experiments were performed with albumin, and they stated that the addition of sodium chloride assisted in the absorption of that substance. Czerny and Latschenberger [6] reported studies on two patients in whom the entire large intestine, or part of it, had been completely cut off from the small intestine. In these they obtained evidence which indicated that dextrose was absorbed. Deucher [7] reported that he gave five enemas to a patient during nineteen hours, each containing 40 Gm. of dextrose. One hundred and fifty-four grams of dextrose was absorbed, constituting 77 per cent of the amount introduced. Reach,[8] experimenting with normal men, found that there was a slight rise in the respiratory quotient, which corresponded to a rise in the peripheral blood sugar after the rectal administration of dextrose. He assumed that there was

2. McNealy, R. W., and Willems, J. D.: Surg., Gynec. & Obst. 49:794, 1929.

3. Scott, E. L., and Zweighaft, J. F. B.: Blood Sugar in Man Following the Rectal Administration of Dextrose, Arch. Int. Med. 49:221 (Feb.) 1932.

4. Goldschmidt, S., and Dayton, A. B.: Am. J. Physiol. 48:419, 1919. Goldschmidt, S.: Physiol. Rev. 1:421, 1921.

5. Voit, C., and Bauer, J.: Ztschr. f. Biol. 5:537, 1869.

6. Czerny, von V., and Latschenberger, J.: Virchows Arch. f. path. Anat. 59:161, 1874.

7. Deucher, P.: Deutsches Arch. f. klin. Med. 58:210, 1897.

8. Reach, F.: Arch. f. exper. Path. u. Pharmakol. 47:231, 1902.

some absorption of dextrose. Zehmisch,[9] working with human beings, gave 152 Gm. of dextrose by rectum and lost 103 Gm. (67.5 per cent), supposedly by absorption. Arnheim[10] gave 50 Gm. of dextrose by bowel to diabetic persons. He was able to recover only 3 Gm. of dextrose after a period of five hours. He did not believe that bacterial action could account for the dextrose that had disappeared. Boyd and Robertson[11] fed seven women on nutrient enemas for from six to seven days. Each day the bowel was washed out and the contents analyzed. Urinary nitrogen was used as a gage of the absorption of nitrogenous substances. They reported that in two cases 100 per cent of the introduced dextrose was absorbed. They lost as much as 61.8 and 81 Gm. of dextrose during twenty-four hours, but recovered the bulk of the protein in the rectal washings. After having incubated dextrose solutions which were contaminated with colon bacilli, they concluded that the dextrose lost by bacterial action was insignificant. They were not able to produce dextrosuria with the amounts they administered. Halasz,[12] working with patients, placed clysters in the large bowel and, in from five to six hours, found that from 50 to 200 Gm. of the dextrose had disappeared. He accounted for only from 0.5 to 1 per cent of the dextrose as lost by bacterial action. Mutch and Ryffell[13] gave four enemas to each of several patients during a twenty-four hour period. Each enema consisted of 450 cc. of 6 per cent dextrose. When the nutrient enemas were well tolerated, they increased the dextrose to 60 Gm. to the pint of solution. Using a "washout" method of experimentation, they concluded that dextrose could be satisfactorily administered by this route to a maximum of 700 calories per day. Hari and Halasz,[14] working with dogs, placed a ligature around the ileocecal valve and, after the introduction of dextrose solution into the rectum, found that the respiratory quotient was nearly always increased. They reported that they were able to produce actual dextrosuria after the rectal administration of dextrose to their animals. Tallerman[15] gave dextrose enemas to seven normal persons and to one patient with functional vomiting. The solution consisted of 60 Gm. of dextrose in 180 cc. of physiologic solution of sodium chloride, or a 33 per cent dextrose solution. He concluded that absorption took place uniformly, the maximum rise in blood sugar occurring in about one

9. Zehmisch, F.: Ausnutzung von Nährklystieren, Halle, C. Nietschmann, 1903.

10. Arnheim, J.: Ztschr. f. diätet. u. phys. Therap. **8**:75, 1905.

11. Boyd, F. D., and Robertson, T.: Scottish M. & S. J. **18**:193, 1906.

12. Halasz, A. V.: Deutsches Arch. f. klin. Med. **98**:433, 1910.

13. Mutch, N., and Ryffell, J. H.: Guy's Hosp. Rep. **66**:223, 1912.

14. Hari, P., and Halasz, A. V.: Biochem. Ztschr. **88**:337, 1918.

15. Tallerman, K. H.: Quart. J. Med. **13**:356, 1919-1920.

hour and twenty minutes with an average rise of 30 mg. per hundred cubic centimeters of blood. Varela and Rubino [16] stressed the necessity of exposing the dextrose solution to the rich venous plexus of the rectal ampulla. They placed 40 per cent dextrose solutions in the rectums of patients and tested the peripheral blood and urine for dextrose. They found that minute amounts were absorbed shortly after the dextrose was introduced, but that soon the colon became irritated and expelled the enema. Carpenter,[17] in two experiments on human beings, gave 30 Gm. of dextrose in 500 cc. of physiologic solution of sodium chloride. Within two or three hours after the injection, the respiratory quotient changed from 0.02 to 0.05. He found that 17.5 Gm. of dextrose was absorbed in one instance and, in the other, 26.3 Gm. Similarly, five hours after the administration of 60 Gm. of dextrose, he found that 34.6 Gm. had apparently been absorbed. The quantitative results were based on the "washout" method, using more than one lavage.

Bingel [18] investigated the absorption of dextrose in diabetic patients. He concluded that only small amounts of dextrose were absorbed. One hour after having placed 35 Gm. of dextrose in the bowel, 31 Gm. was recovered in the stool. Bingel incubated fecal material with added dextrose, and claimed that the dextrose lost was almost as great as that supposed to have been absorbed.

Franke and Wagner [19] gave concentrated enemas to dogs. They used 25 Gm. of dextrose in a 50 per cent solution. They determined the peripheral blood sugar at fifteen, thirty, forty-five and sixty minute intervals, and found the highest rise of blood sugar to be 20 mg. per hundred cubic centimeters. They concluded that dextrose enemas had little, if any, effect on the peripheral blood sugar. Levi [20] gave dextrose to fasting normal, diabetic and postoperative patients. He used 500 cc. of from 10 to 16 per cent dextrose solutions and found that patients varied as to their reaction, but, in general, took up only slight amounts of the dextrose.

McNealy and Willems, in 1929, working with isolated loops of the large and small bowel of the dog, gave this problem renewed interest. They introduced known amounts of dextrose into the colon or ileum and studied the changes quantitatively. They also studied the ileal, colic and peripheral venous blood sugar during the experiment. They used a 5 per cent dextrose solution and found that from 0.3 per cent

16. Varela and Rubino: Med. Klin. **18**:831, 1922.

17. Carpenter, T. M.: Human Metabolism with Enemata of Alcohol, Dextrose, and Levulose, publ. 369, Washington, D. C., Carnegie Institution, 1925.

18. Bingel, A.: Therap. d. Gegenw. **46**:436, 1905.

19. Franke, W., and Wagner, R. J.: J. Metab. Research **6**:375, 1924.

20. Levi, D.: Brit. J. Surg. **15**:282, 1927.

to as much as 2.6 per cent of the dextrose was lost from the large bowel, with a corresponding loss of from 23.3 to 59 per cent from the ileum over the same time interval. They found that the colic venous blood sugar fell, while the blood sugar from the ileal vein in the ileal experiments rose. They concluded that a 5 per cent dextrose solution was of little or no nutritional value when administered rectally. They suspected the presence of an incompetent ileocecal valve as the basis for some of the experimental and clinical success reported in the literature. Later,[21] they reported the effect of sodium chloride on dextrose absorption from the colon and found that, although the percentage of absorption was slightly greater, it was not sufficient to be of practical importance.

Pressman [22] gave 33 per cent dextrose solutions by rectum and by mouth to human beings and observed the blood sugar curves for a period of four hours. He found that the peripheral blood sugar level fell after the introduction of dextrose into the rectum without any significant preliminary rise. He recovered an average of 24 per cent from the colon after four hours. He stated that 90 per cent of the dextrose was destroyed by incubation with feces in seven hours. De Takáts,[23] in 1931, gave 1,000 cc. of 5 per cent dextrose to patients under the skin, by mouth and by bowel. The blood sugar level rose after introduction of dextrose under the skin and by mouth. When the dextrose was given by rectum, the blood sugar fell during a period of two hours. He noted that no dependence could be placed on the amount absorbed by rectum, and that insulin reactions occurred when this method of entry was depended on in the diabetic person.

Scott and Zweighaft, in experiments on medical students, investigated the blood sugar changes following the rectal administration of dextrose. They found no rise in the peripheral blood sugar after the administration of 180 cc. of a 15 or 30 per cent solution of dextrose. They also found that, after the rectal introduction of 200 cc. of a 10 per cent dextrose solution, the blood sugar level fell about 10 mg. per hundred cubic centimeters, while after the administration of 400 cc. of a 10 per cent dextrose solution the fall was about 7.5 mg. per hundred cubic centimeters. They concluded that the fall in blood sugar was due to pancreatic action or chance variation. They were able to recover from 25 to 50 per cent of the dextrose they had administered.

Since this paper went to press, Perusse [23a] has published data that led him to make the following statement: "We can then perhaps come

21. McNealy, R. W., and Willems, J. D.: The Absorption of Dextrose from the Colon: II. A Study of the Effects of Chemical Excitants and of Stimulants of Dextrose Enema, Arch. Surg. **22**:649 (April) 1931.

22. Pressman, J. J.: Am. J. M. Sc. **179**:520, 1930.

23. de Takáts, G.: Am. J. Surg. **11**:39, 1931.

23a. Perusse: Surg., Gynec. & Obst. **54**:770, 1932.

to the tentative conclusion that 1 per cent glucose solution is the ideal for restoring water balance and for supplying some degree of nutrient."

COMMENTS ON PREVIOUS EXPERIMENTAL AND CLINICAL OBSERVATIONS

There are certain obvious objections to the methods used by some of the investigators whose work has been cited. The "washout" method has been widely criticized on the ground that it fails to consider adequately: (1) bacterial action on the introduced dextrose; (2) the fact that reverse peristalsis may carry the solution beyond the reach of recovery, or even through an incompetent ileocecal valve into the ileum where absorption may occur.

Recent investigations of the responsibility of bacterial action for the loss of some of the dextrose from the large bowel give contradictory results. Cori,[24] in 1925, incubated the small intestines with known contained quantities of dextrose for from three to five hours at 37 C., and he concluded that the amount of dextrose lost in this part of the bowel by bacterial action was so small that it was negligible. Bingel[18] incubated fecal material with dextrose and claimed that the quantity lost through bacterial action was equal to the amount supposed to have been absorbed. Pressman[22] incubated dextrose and feces for seven hours. He found that nearly 90 per cent of the dextrose had been destroyed. McNealy and Willems[2] avoided the question of loss of dextrose in this manner by using a short period of experimentation.

Experimental and clinical data demonstrate that the incompetency of the ileocecal valve may play a large part in those instances in which absorption has been demonstrated. Cannon[25] found that large injections into the colon go into the small intestine by means of antiperistalsis. Case[26] stated that the true cause of insufficiency of the ileocecal valve is overdistention of the right half of the colon. He found insufficiency in one sixth of 1,500 cases of constipation, observed roentgenologically. A personal communication from Pendergrass[27] supports this observation.

Other methods for the solution of the problem of dextrose absorption have been offered. Salvesen[23] reported a fall in the inorganic phosphates following injection of dextrose into the blood stream. Bollinger and Hartman[29] and Harrop and Benedict[30] have also

24. Cori, C. F.: J. Biol. Chem. 66:691, 1925.
25. Cannon, W. B.: Am. J. Physiol. 6:251, 1902.
26. Case, J. T.: Arch. Roentgen Ray 19:375, 1915.
27. Pendergrass, E. P.: Personal communication.
28. Salvesen, H. A.: J. Biol. Chem. 56:443, 1923.
29. Bollinger, A., and Hartman, F. W.: J. Biol. Chem. 64:91, 1925.
30. Harrop, G. A., Jr., and Benedict, E. M.: J. Biol. Chem. 59:683, 1924.

reported changes in the inorganic phosphates of the serum after injections of dextrose. I am not aware that the level of blood inorganic phosphates has been used as a measure of the absorption of dextrose from the colon. The use of the respiratory quotient in this type of experiment is open to some question unless the results are striking. Brodie,[31] in 1910, demonstrated that the introduction of distilled water into the bowel might cause increased oxygen consumption.

Diabetic patients show a marked variation in the readiness with which the liver glycogen may be mobilized in response to nervous stimulation and to mechanical pressure changes in the intestinal tract. This factor, as brought out by Smith[32] in 1930, may influence the respiratory quotient. Furthermore, the sensitive patient may show a slight rise in the sugar in the blood from the mere insertion of a rectal tube with a later and more marked rise in the blood sugar if the amount of solution introduced into the rectum is sufficient to cause marked distention of the intestine. This reversal of glycogen synthesis may be responsible for the increase in the respiratory quotient noted.

So far as I have been able to ascertain from a careful search of the literature, no one whose experiments have been controlled has found the marked alterations of the peripheral venous blood sugar after the rectal administration of dextrose which are encountered when dextrose is given by mouth.

Cori,[33] after investigation of the alimentary absorption of dextrose, has concluded recently that the peripheral blood sugar curve is not a measure of intestinal absorption. Magee and Reid,[34] on the contrary, have concluded that the dextrose curve is an index of intestinal absorption. They compared the portal and systemic blood during the absorption of dextrose from the intestine and found that the pre-absorption values were practically always identical, but that about three minutes after the ingestion of the solution the portal blood sugar had risen about 20 mg. higher than the systemic blood sugar. These relative positions were approximately maintained until the end of the experiment. They assumed that the difference between the curves could be interpreted to represent the balance between the effects of hepatic function and of tissue metabolism on the blood sugar, and the systemic (venous) curve afforded as good an index of the rate of absorption as the portal curve.

31. Brodie, T. G.; Cullis, W. C., and Halliburton, W. D.: J. Physiol. **40**:173, 1910.

32. Smith, B.: California & West. Med. **33**:857, 1930.

33. Cori, C.: Physiol. Rev. **11**:143, 1931.

34. Magee, H. E., and Reid, E.: J. Physiol. **73**:163, 1931.

The strength of the solution used in the bowel in attempting to demonstrate absorption has varied considerably. Goldschmidt [35] observed that the absorption from the entire length of the intestinal tract, so far as sodium chloride was concerned, involved a similar mechanism, and that the mechanism could be qualitatively explained by the known laws of osmosis. Theoretically, a 4.9 per cent dextrose solution has the same osmotic tension as physiologic solution of sodium chloride. Hausman [36] demonstrated that hypertonic solutions may produce undesirable results. He caused death in rats through the withdrawal of large quantities of water into the peritoneal cavity by means of a 50 per cent solution of dextrose. Certain of the variations in the results of different investigators may be explained by the difference in the concentrations of dextrose which were used.

In consideration of the literature and experimental data covered in this résumé, an experiment on the problem of dextrose absorption from the intestinal tract in the normal, the pancreatectomized and the insulinized animal was outlined which:

(1) Eliminated the ileum and isolated the colon and rectum.

(2) Considered the absorption of isotonic as well as hypertonic dextrose solution in the normal dog and isotonic dextrose solutions in the pancreatectomized, hyperglycemic, and in the insulinized, hypoglycemic, dog.

(3) Eliminated the possibility of intestinal putrefaction or bacterial action as a great factor in the loss of dextrose by careful cleansing of the bowel and by limiting the time of the experiment.

(4) Measured the absorption of dextrose in three ways simultaneously:
    (*a*) recovery and washings
    (*b*) peripheral blood sugar studies
    (*c*) colonic blood sugar studies

(5) Was controlled in the following ways:
    (*a*) Similar experiments were made with loops of ileum of equal length where dextrose absorption is known to take place.
    (*b*) An inert substance (paraffin oil) was introduced into the colon and rectum to control possible alterations in the blood sugar due to mere filling of the bowel.
    (*c*) Loss of dextrose through bacterial action and mere handling was determined by the incubation of a known dextrose solution within a colon and rectum removed from a freshly killed animal, washed and prepared in a similar manner over the same time period.
    (*d*) The possible presence of large amounts of nondextrose copper-reducing substances was eliminated by the introduction of distilled water into the colon and rectum under like methods and titration of the recovered solution by the same method used in the colonic dextrose determinations.

35. Goldschmidt, S.: Physiol. Rev. **1**:421, 1921.
36. Hausman, W.: Wien. klin. Wchnschr. **38**:332, 1925.

In the experimental work twenty-four dogs were used. They were of mongrel breeds, and weighed from 7 to 32 Kg. The average weight was about 10 Kg. All dogs received their last feedings at 4 o'clock on the day before the experiment. Sodium amytal (sodium iso-amyl ethyl barbiturate) anesthesia was employed, 50 mg. per kilogram of body weight being introduced intraperitoneally. Nearly all the dogs went to sleep without excitement and slept quietly throughout the entire experiment with deep, slow respiration, although there was an occasional exception to this.

The abdomen was opened, and the appendix with the adjacent ileum was mobilized and brought into the wound. Two ligatures were passed around the ileum at its cecal junction and tightly tied. The tip of the appendix was then removed, and a glass cannula with an attached fenestrated rubber tube was inserted through the appendix into the cecum. The fenestrated rubber tube prevents collapse of the bowel for a distance of about 3 inches. Two ligatures were used to fasten the stump of the appendix about the cannula. Another rubber tube was attached to the end of the cannula which projected from the appendical stump.

The colon was washed out throughly by running warm tap water into the appendical cannula by means of a funnel. When the water coming from the rectum was clear, a tube similar to that in the cecum was inserted into the rectum. Leakage around the tube was prevented by means of a purse-string suture placed in the rectal sphincter. The colon was again flushed with warm tap water. Any fluid remaining was then forced out by gently passing air through the appendical cannula and elevating the head of the table. The operative procedure rarely took longer than thirty minutes.

Specimens of blood were taken from one of the veins draining the colic blood and from the exposed femoral vein. After the colon was carefully evacuated so that the bowel was collapsed, the rectal tube was clamped, and a dextrose solution of desired strength and known amount was allowed to run into the system at a pressure not exceeding 150 mm. of the solution. When the bowel appeared to be full, but not unduly distended, the appendical clamp was closed. The quantity of solution introduced varied with the size of the animal, 158 and 238 cc. being the lowest and highest amounts used. All solutions were warmed to 38.5 C. before being placed in the bowel. The abdominal incision was then closed, the appendical cannula extending through the closed wound.

Specimens of blood from the femoral vein were taken at half hour intervals. At the end of two hours the last specimen was taken, the abdomen again opened, and a specimen withdrawn from the colic vein. Difficulty in the control of hemorrhage from the colic vessel prevented the withdrawal of blood at more frequent intervals. Following the collection of the blood specimens, the solution remaining within the bowel was forced through the rectal cannula into a beaker by means of air. The head of the table was again elevated in order to facilitate the recovery of fluid. The bowel was flushed with 250 cc. of distilled water, this solution also being forced out into a second beaker by means of air and elevation of the head of the table. It is of interest that, of the 250 cc. of wash water introduced at this time, it was not unusual to recover all 250 cc. Occasionally a few cubic centimeters was lost and, at other times, 2 or 3 cc. more was recovered. A series of experiments on the ability to recover known amounts of fluid by this method showed that the error averaged 2 per cent ($\pm$ 2 per cent).

At the close of the experiment the animal was killed, and a section of the colon was removed for microscopic examination.

In the experiments on the ileum, loops approximately equal in length to the colon were isolated near the terminal portion. The loops were cannulated with Paul tubes with attached fenestrated rubber tubes. Blood specimens were withdrawn from the large ileal vein opposite the selected loop.

The pancreatectomies were performed under sodium amytal anesthesia. The operations were done with aseptic technic, and the pancreas was removed with no injury to the duodenal vessels. A specimen of the blood sugar during fasting was taken before pancreatectomy, the morning following and each morning thereafter. When the blood sugar level during fasting indicated marked hyperglycemia, the absorption experiments were performed. Blood sugar levels prior to the dextrose absorption experiments varied from 225 to 325 mg. per hundred cubic centimeters. The interval between pancreatectomy and the dextrose absorption experiment varied from two to four days.

For the hypoglycemic animals, the following method was used. Specimens of blood from the peripheral and colic veins were taken, following which 10 units of insulin per kilogram of body weight was given subcutaneously. After a lapse of one-half hour, blood was again taken from the colic and femoral veins and the dextrose solution introduced, after which the absorption experiment was carried out in the usual manner.

All dextrose solutions were prepared from Bacto-dextrose. The dextrose in each instance was weighed and diluted to volume, after which the solution was titrated for the concentration of dextrose present. The latter figure is used throughout in the final calculations.

The effect on the blood sugar level of the introduction of an inert substance (paraffin oil) into the colon was observed in several experiments. These experiments were performed in the same manner as the usual absorption experiment, except that warmed paraffin oil was allowed to flow into the colon instead of the usual dextrose solution.

The effect of bacterial action and handling on a known amount of dextrose solution in a completely excised colon from a freshly killed animal was tested. The excised colon was washed and prepared in a manner similar to that used in the intact animal. Seventy-five cubic centimeters of an approximately 5 per cent dextrose solution containing 3.31 Gm. of dextrose was placed within the bowel, and the entire preparation placed in a beaker and incubated at 37.5 C. for two hours. At the end of that time the solution was recovered. The bowel and beaker were washed with 250 cc. of distilled water, and the dextrose content of each solution was determined.

All solutions recovered, as well as washings, were quantitatively analyzed by the Benedict method [37] immediately after completion of the experiment in order to eliminate the possibility of loss of dextrose through standing and bacterial action. Some of the solutions, especially when hypertonic dextrose was used, contained mucus, so that it was necessary to filter or centrifugate them before titration.

Because of the fact that the Benedict method is based on the reduction of copper, it was necessary to determine the possible presence of nondextrose copper-reducing substances in the solutions exposed to the intestinal mucous membrane. For this experiment the colon of an anesthetized animal was prepared in the usual manner, and 200 cc. of distilled water was introduced. After the lapse of two hours, the solution was withdrawn in the usual way and titrated by the Benedict method. [57]

37. Benedict, S. R.: The Detection and Estimation of Glucose in the Urine. J. A. M. A. **57**:1193 (Oct. 7) 1911.

All blood sugar determinations were made in duplicate by the Hagedorn and Jensen micromethod.[38] In several of the earlier experiments, Dr. Leon Jonas made simultaneous determinations by the Folin-Wu method. Except for the slightly lower level of the former determinations, the results were approximately the same.

RESULTS

The Absorption of a 5 Per Cent Dextrose Solution from the Ileum.— In tables 1 and 1a the results from three experiments are given. In every experiment water and dextrose were absorbed, and the concentration of the dextrose in the loop fell. There is a close relationship

TABLE 1.—*Five Per Cent Dextrose Solution in Ileum of Normal Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out. Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, In Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
815	11.2	240	4.1	214	3.6	—26	—10.4	9.84	7.70	0.41	8.11	1.73	82.4	17.6
1067	13.3	184	4.8	129	3.4	—55	—29.8	8.83	4.39	0.39	4.78	4.05	54.2	45.8
1068	7.8	158	4.5	138	3.95	—20	—12.6	7.11	5.45	0.35	5.80	1.31	81.6	18.4
Mean........		194		160		—34	—17.6	8.59			6.23	2.36	72.7	27.8

TABLE 1a.—*Peripheral and Ileal Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Ileum of Normal Dog*

Dog No.	Peripheral Venous Sugars, Mg. per 100 Cc.					Ileal Venous Sugars, Mg. per 100 Cc.	
	Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
815	83	85	86	88	90	85	97
1067	120	139	139	142	142		
1068	91	130	132	118	114	101	131

between the removal of water and absorption of dextrose, but dextrose apparently was absorbed more rapidly than water. The mean loss of fluid was 17.6 per cent, and the mean loss of dextrose, 27.3 per cent.

The peripheral venous sugars showed a tendency to rise. There is no correlation between the percentage of absorption of dextrose and the change in either the peripheral venous or the ileal blood sugars. In fact, of the two experiments in which ileal venous sugars were determined, the larger amount of dextrose absorption was associated with the smaller change in the ileal venous sugar.

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38. Hagedorn, H. C., and Jensen, B. N.: Biochem. Ztschr. **135**:46, 1923; **137**:92, 1923.

The Absorption of a 5 Per Cent Dextrose Solution from the Colon.—
Eight experiments are tabulated in tables 2 and 2a. There is a striking
difference in the mean loss of fluid in these experiments as compared
to the ileal experiments. In only one of the eight experiments did the
percentage of absorption of water exceed the minimum percentage of
absorption in the first group.

Although the actual amount of dextrose introduced was greater in
nearly every experiment, the mean percentage of absorption of dextrose

TABLE 2.—*Five Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out. Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, in Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
383	32.0	230	4.9	214	4.4	−16	− 6.9	11.27	9.42	0.60	10.02	1.25	88.9	11.1
652	17.3	230	4.5	220	4.0	−10	− 4.3	10.35	8.80	0.57	9.37	0.98	90.6	9.4
761	16.2	200	5.0	168	4.9	−32	−16.0	10.00	8.23	0.80	9.03	0.97	90.3	9.7
655	12.6	204	5.0	199	4.5	− 5	− 2.4	10.20	8.96	0.32	9.28	0.92	91.0	9.0
710	19.1	238	5.0	224	4.8	−14	− 5.9	11.90	10.75	0.27	11.02	0.88	92.6	7.4
834	10.6	190	4.7	184	4.5	− 6	− 3.1	8.93	8.28	0.21	8.49	0.44	95.1	4.9
942	15.9	155	5.0	141	5.0	−14	− 9.0	7.75	7.05	0.36	7.41	0.34	95.5	4.5
893	9.7	154	5.0	148	4.9	− 6	− 3.8	7.70	7.25	0.32	7.57	0.13	98.4	1.6
Mean........		200		187		−13	− 6.4	9.76			9.02	0.74	92.8	7.2

TABLE 2a.—*Peripheral and Colic Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
	Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
383	96	...	93	...	103	95	78
652	70	. .	70	...	...	83	76
761	140	...	140	...	136	135	138
655	150	..	...	...	124	142	112
710	106	105	100	88	85	101	100
834	105	108	108	99	108	105	107
942	...	127	108	121	124	148	121
893	109	130	126	121	120	113	118

from the colon was decidedly less. There are, however, a slightly
greater mean loss of dextrose than of water and a tendency for the
concentration of the solution to fall slightly. Considered from the
standpoint of actual loss of dextrose over a two hour period, however,
the amount is indeed small, 90 per cent or more having been recovered
after a two hour period.

In four animals the peripheral venous sugar changed very little.
The changes that did occur were not always in the same direction. In

three experiments the initial blood sugar was high, a condition that is believed to be due to the excitation associated with the induction of anesthesia. The colic venous sugar was likewise high in these animals. There is no indication from the estimations of the colic venous sugar that dextrose was being absorbed rapidly.

Taken as a whole, the data do not support the hypothesis that any considerable amount of dextrose is absorbed in this type of experiment.

Histologic studies of the colon at the conclusion of the experiment showed a normal bowel.

TABLE 3.—*Seven Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out. Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, In Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
5S6	12.2	200	6.9	252	5.2	+52	+26.0	13.80	13.23	0.42	13.65	0.15	98.9	1.1
601	12.0	200	6.9	240	4.9	+40	+20.0	13.80	11.76	0.22	11.98	1.82	86.9	13.1
Mean........		200		246		+46	+23.0	13.80			12.81	0.98	92.9	7.1

TABLE 3a.—*Peripheral and Colic Venous Sugars Following Introduction of 7 Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
	Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
5S6	9S	104	104	109	106	107	110
601	S7	95	100	102	94	S7	96

The Absorption of a 7 Per Cent Dextrose Solution from the Colon. —It was considered advisable to repeat the experiments on the colon, with hypertonic solutions of dextrose. In tables 3 and *3a* are reported two experiments in which an approximately 7 per cent solution was used. At the end of the two hour period the amount of fluid in the large bowel was greater than that introduced. No definite conclusions can be drawn from the two experiments, but the range of dextrose absorption is within the limits of that obtained when a 5 per cent solution was used.

The peripheral and colic venous sugars tended to rise slightly, but there is a complete lack of correlation between the actual amount of dextrose lost and the changes in the peripheral blood sugar levels.

The histologic studies of the colon removed at the conclusion of the experiment showed only a slight increase in vascularity as evidenced by the greater number of filled capillaries.

The Absorption of a 10 Per Cent Dextrose Solution from the Colon.—In tables 4 and 4a are tabulated the results obtained from two experiments in which a more concentrated solution was used. As would be expected, the increase in the fluid content of the loop was even greater than when a 7 per cent solution was used. The concentration of dextrose was reduced, but this was largely due to the diluting effect

TABLE 4.—*Ten Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out, Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, in Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
20	11.8	155	9.7	214	6.0	+56	+35.4	15.33	12.84	0.55	13.39	1.94	87.4	12.6
410	17.0	250	9.7	339	6.2	+89	+35.6	24.25	21.02	0.55	21.57	2.68	89.0	11.0
Mean........		204		276		+72	+35.5	19.79			17.48	2.31	88.2	11.8

TABLE 4a.—*Peripheral and Colic Venous Sugars Following Introduction of 10 Per Cent Dextrose Solution in Colon of Normal Dog*

	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
Dog No.	Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
20	95	80	95	87	83	94	107
410	90	95	88	85	82	83	101

of the inflowing fluid. The mean amount of dextrose lost is slightly greater than that lost when a 5 per cent solution was used.

The peripheral venous sugar was lower at the conclusion of the experiment than at the beginning, while the colic venous sugar had increased in each experiment by 13 mg. per hundred cubic centimeters of blood.

The sections of the bowel removed at the conclusion of the experiment were similar to those removed from the previous group in that the only evidence of change was an increase in the number of filled capillaries.

The Absorption of a 5 Per Cent Dextrose Solution from the Colon of the Pancreatectomized Dog.—Five experiments are reported in tables 5 and 5a. The hyperglycemia in these animals was considerably greater

than that of the animals in group 2, who were excited during the induction of the anesthesia. The mean percentage of fluid absorbed was slightly greater than when a similar concentration of dextrose was placed in the colon of the normal dog. However, if the data from dog 387 are eliminated, the percentage of fluid absorbed is within the range of the normal animals. There is no evidence that dextrose is more rapidly absorbed under the conditions of this experiment. The percentage range of dextrose absorption in the five experiments is large,

TABLE 5.—*Five Per Cent Dextrose Solution in Colon of Pancreotectomized Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out, Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered In Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
387	9.8	144	3.75	110	3.3	−34	−23.6	5.40	3.63	0.83	4.46	0.94	82.6	17.4
390	9.9	232	4.7	220	4.7	−12	−5.1	10.90	10.34	0.56	10.90	0.00	100.0	0.0
362	9.9	171	4.95	162	4.7	−9	−5.2	8.46	7.61	0.58	8.19	0.27	96.8	3.2
450	9.9	207	4.5	198	3.7	−9	−4.3	9.31	7.33	0.33	7.66	1.65	82.3	17.7
540	10.9	233	4.8	220	4.3	−13	−5.5	11.18	9.46	0.72	10.18	1.00	91.1	8.9
Mean........		197		182		−15	−9.3	9.05			8.25	0.77	90.6	9.4

TABLE 5a.—*Peripheral and Colic Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Colon of Pancreatectomized Dog*

Dog No.	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
	Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
387	278	261	276	265	260	250	290
390	315	299	311	299	...	303	268
362	225	196	175	220	...	244	261
450	325	310	315	298	284	263	295
540	258	253	271	279	271	252	261

but the mean dextrose absorption is approximately the same as in the previous experiments. Again there is a tendency toward a reduction in the concentration of the dextrose in the colon.

The peripheral and colic venous sugars show no consistent changes. There is a tendency for the peripheral venous sugar to decrease, but in dog 540 it increased. The colic venous sugars rose in four of the five experiments, and there appears to be some correlation between the percentage of absorption of dextrose and the rise in the colic venous sugar. In the one experiment in which a fall occurred in the colic venous sugar, there was no evidence of dextrose absorption.

The sections of the colon were entirely normal.

The Absorption of a 5 Per Cent Solution of Dextrose from the Colon of the Hypoglycemic Dog.—The results in two animals made hypoglycemic by the subcutaneous injection of 10 units of insulin per kilogram of body weight one-half hour before beginning the experiment are reported in tables 6 and 6a. The percentage of fluid absorbed is small indeed, the lowest for any group in which approximately isotonic solutions were used. The striking feature, however, is the

TABLE 6.—*Five Per Cent Dextrose Solution in Colon of Insulinized (Hypoglycemic) Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out, Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, In Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
161	16.6	240	5.2	228	4.2	−12	− 5.0	12.50	9.57	0.26	9.83	2.67	78.7	21.3
759	17.2	240	4.95	238	3.8	− 2	− 0.8	11.88	8.97	0.29	9.26	2.62	77.9	22.1
Mean........		240		233		− 7	− 2.9	12.19			9.54	2.64	78.3	21.7

TABLE 6a.—*Peripheral and Colic Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Colon of Insulinized (Hypoglycemic) Dog*

Dog No.	Before Insulin	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
		Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
161	84	81	72	55	41	29	74	37
759	135	99	78	67	55	57	85	

relatively rapid absorption of dextrose, a mean of 21.7 per cent of that injected being lost in the two hour period. In these experiments dextrose was leaving the colon much more rapidly than was water.

The peripheral and colic venous sugars fell throughout each experiment so that, even though considerable dextrose was absorbed, the insulin was sufficient to prevent it from maintaining a constant sugar level. It must be considered, however, that the dose of insulin was unusually large. This dosage was used purposely in order to determine whether the rate of absorption from the colon could be increased under the conditions of a marked blood dextrose deficit.

The Effect of the Introduction of an Inert Substance (Paraffin Oil) into the Colon on Blood Sugar Levels.—Two experiments were per-

formed (table 7) in each of which paraffin oil similar in volume to the dextrose used in the earlier experiments was placed in the isolated colon. Specimens of blood were removed from the peripheral and colic veins. These showed slight variations. The colic venous sugars tended to go to lower levels at the end of the two hour period.

Bacterial Action.—The effect of bacterial action and handling on a known amount of dextrose solution in a completely excised colon, from a freshly killed animal, washed and prepared in a manner similar to the method used in the intact animal, was also tested. The 75 cc. of a 4.7 per cent solution of dextrose which was introduced contained 3.31 Gm. of dextrose. The bowel and its contents were placed in a beaker and incubated at 37.5 C. for two hours. At the end of that period, 70 cc. of the solution was recovered which contained 3.08 Gm. of dextrose. The washings contained an additional 0.14 Gm. of dextrose, bringing

TABLE 7.—*Peripheral and Colic Venous Sugars Following Introduction of Paraffin Oil in Colon of Normal Dog*

Dog No.	Weight, Kg.	Oil, Cc.	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
			Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	End
1034	8.8	132	102	103	103	96	104	102	92
1046	7.7	154	113	115	114	122	112	106	101

the total amount recovered to 3.22 Gm. The dextrose lost through possible bacterial action and failure to recover was estimated at 2.6 per cent of the quantity introduced.

Determination of Nondextrose Copper-Reducing Substances in the Solutions Exposed to the Mucous Membrane of the Bowel.—Of the 210 cc. of tap water introduced into the colon of the living dog, but 150 cc. of fluid was recovered after the lapse of two hours. Titration was done by the Benedict method.[37] It was impossible to arrive at an end-point by using the entire 150 cc. recovered from the loop. Calculated at this point, the concentration of the reducing substances would be less than 0.03 per cent, and, from the color of the copper solution remaining, it would be safe to state that the amount was even lower than this. Even at the former level, the quantity is insignificant.

This experiment likewise demonstrates that tap water is readily and quickly taken up by the colon to the extent of 28.5 per cent in this one case.

Venous blood sugar determinations were made as well in this dog. The determinations of the peripheral and colic venous blood sugar showed little change.

COMMENT

It is evident from these experiments that there is a marked difference in the ability of the ileum and colon of the dog to absorb dextrose. In a two hour period, the normal anesthetized dog being used, the rate of absorption of dextrose from solutions varying from approximately 5 to 10 per cent was indeed small. The percentage of dextrose absorption is slightly greater than that given by McNealy and Willems [2] for 5 per cent solutions, but this may be due to the use of the large rectal ampulla. There appears to be a slightly greater absorption when 10 per cent solutions are used, but even here the actual amount absorbed was so small that even though the same rate could be maintained for a twenty-four hour period, the total dextrose absorbed would amount to only 27.7 Gm.

In two of the pancreatectomized animals the percentage absorption was considerable, but when calculated for the total amount absorbed, it is of little significance, a mean in all the pancreatectomized dogs of only 0.77 Gm. being absorbed over the two hour period.

It is interesting to note that, when a definite blood sugar deficit was maintained, as in the experiments on the hypoglycemic dogs, the percentage of absorption of dextrose was higher than in any of the colonic experiments and approximated the rate of absorption from the ileum. It would appear from these experiments that there may be some foundation in the observation of clinicians that diabetic persons in shock are improved by rectally administered dextrose. However, when time is an essential factor, it would not be wise to place the sole reliance on this method of administration of dextrose because the absorption is so slow.

The findings of McNealy and Willems [2] in regard to the rate of water removal when solutions of dextrose are placed in the large bowel have been confirmed. Tap water is absorbed much more rapidly. With the exception of one animal (dog 387, table 5), nothing approximating this rate of removal was observed in any of the experiments on the colon in which dextrose was used. Clinical experience has demonstrated that this is also true in man.

The blood sugar studies indicate that they are of little use as an indication of absorption where the rate of absorption is small. The findings in normal subjects presented in this paper are in essential agreement with those of Scott and Zweighaft.[3] There appears to be no direct correlation between the amount of dextrose absorbed and the peripheral blood sugar level. This may be due to the slow rate of absorption and to the stimulation of some mechanism which increases dextrose withdrawal from the blood stream. In the experiments in

which 7 and 10 per cent solutions of dextrose were placed in the colon, and in the pancreatectomized dogs, the colic venous sugars show some correlation with the amount of dextrose removed from the colon during the two hour period.

SUMMARY

Dextrose solutions are absorbed at a low rate when placed in the entire colon of the dog. Hypertonic solutions (10 per cent) are absorbed little faster than are isotonic solutions. When a marked dextrose deficit occurs in the blood, dextrose can be absorbed from the colon approximately as rapidly as it can be from a low ileal loop of the noninsulinized dog. The presence of dextrose in the solution in the colon, in the concentration used, causes a retardation in the rate of water absorption. The total amount of dextrose which can be administered and absorbed from the colon under the best conditions would appear to be too small for any considerable immediate therapeutic effect.

SELECTIVE STAINING OF DISEASED AREAS IN CARTILAGE BY INTRA-ARTICULAR INJECTION OF DYES

AN EXPERIMENTAL CADAVER STUDY, WITH SPECIAL REFERENCE TO ARTHROSCOPY

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The intra-articular injection of dyes is not a new procedure, though practiced only from the experimental standpoint to determine the absorptive capacity of the synovial membrane and the paths of absorption. A review of the literature indicates that no attention has been paid to the gross staining of cartilage by dyes. Tillmanns, in 1876, injected berlin blue into the bony canals of the amputated femurs of his experimental animals, after cutting away the bony plate that intervenes between the femur and the joint cavity. He intended to study the absorptive power of the synovia, without injuring either synovia or capsule. In seven cases, he noted a superficial staining of cartilage, easily washed out by a stream of water. Schreiber of Tübingen, in 1904, in analyzing the constituents of Belchier's madder, noted that purpurin, injected into the dorsal lymph sac of the frog, stained cartilage vitally a purple hue.

The gross staining reactions of cartilage in disease, as in jaundice and hematoporphyrinemia, are interesting. One deals here with pigments circulating in blood. Whether this is the case in ochronosis, which stains cartilage blackish, is still mooted. It is affirmed in all textbooks of pathology that in jaundice cartilage is not stained *intra vitam*. We have had several occasions to verify this. Schmorl has shown that the degenerated cartilage of intervertebral disks does take up the icteric stain *intra vitam*. It is the custom in the Pathologic Institute in Dresden to remove the entire right femur for examination. On the right side. then, in all cases of jaundice, the cartilage of the patella, of the femoral and tibial condyles and even of the menisci was stained green, the intensity of color varying with the length of exposure to air. When the left

or untouched knee joint was opened or was examined through the arthroscope, the cartilage and menisci were noted as definitely not stained.

This work was undertaken as a collateral study to arthroscopy,[1] following a suggestion of Professor Schmorl that it would be interesting to observe through the arthroscope the formation of arthritis experimentally produced by the use of colored irritants. I determined to test the general effect of a dye on the cartilage of cadavers recently deceased. I used the standard laboratory solutions of the various dyes used for tissue staining, diluted about 1 : 10 with water. The dye used was injected into the joint, usually the knee joint, and was immediately washed out by continuous irrigation. In many cases, the joint was then examined through the arthroscope to determine just what had happened in the interior of the joint. After a thorough examination, the findings were verified by opening the joint.

RESULTS

The following is a report of the work done.

Eosin.—Eosin apparently stains eroded areas on cartilage selectively and instantaneously; that is, normal or almost normal cartilage does not stain. The usual eroded areas on the under surface of the patella and on top of the intercondyloid notch stain particularly well. The stain is deep in the eroded areas but does not extend to bone. The greater.the erosion, the deeper is the stain. Degenerated areas in cartilage, showing no particular erosion, stain from a light to a deep pink, though with not as great a selectivity as areas of erosion. Areas of "Wucherung" or overgrowth of new cartilage or fibrous tissue may stain better and deeper than small areas of erosion. Eosin, injected into a normal joint, will not stain cartilage. When the joint is opened and eosin is poured over the cartilage of the opened joint, all cartilage, whether normal, degenerated or eroded, stains almost uniformly. This may be due to exposure to air—the only explanation we can offer thus far for this phenomenon of paradoxical staining. Acid, such as hydrochloric acid, injected into the joint previous to the injection of the dye does not alter the staining powers of the dye.

Most of the joints into which eosin was injected were those of elderly people having arthritis of varying degree. Not only does cartilage stain, but it is seen that the synovial membrane, the crucial ligaments and the semilunar cartilages (menisci) also stain. The semilunar cartilages stain variously, best on their superior and inferior surfaces, but never in their depths. The staining is more pronounced if the

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1. Burman, M. S.: Arthroscopy or the Direct Visualization of Joints. An Experimental Cadaver Study, J. Bone & Joint Surg. **13**:669 (Oct.) 1931.

cartilage is degenerated, and if the inner free edge is irregular and fuzzy. The synovial membrane does not stain uniformly or deeply, but in scattered areas, sometimes more or less diffusely, not depending apparently on sites of degeneration. The infrapatellar fat pad has been noted to be stained through and through, indicating that there is a rapid diffusion of the dye through the synovia. Free synovial villi stain a delicate pink at times. The crucial ligaments, especially the anterior crucial ligament. stain only slightly. The color does not deepen on standing, when the opened joint is exposed to air.

The stain is always superficial and is present only in the upper cell layers of cartilage. Light scraping of the cartilage with a knife removes the stained areas easily and indicates the superficialness of the stain.

If hematoxylin is injected into the joint first and then eosin, after the hematoxylin has been washed out it is noted that the colors may mix or be separate, or that the pink of the eosin may overlie a clearly underlying blue of the hematoxylin. If, in the opened joint, hematoxylin is poured over a previously eosin-stained joint, one can see the blue of the hematoxylin overlying the pink of the eosin, with no tendency to fusion of colors. Each stain is separate. If in the opened knee joint, one half of the tibial condyles are stained with alcoholic eosin and one half with watery eosin, one notes that the resultant stains are uniform and identical.

Occasionally, when the dye is injected as from an inner puncture, the dye is noted to be confined to the inner half of the joint. This may be due to the fact that the joint is divided in halves by fat or adhesions that prevent the further spread of the dye.

Alcoholic eosin was injected into a knee joint in each of two adult rabbits. There was no staining of the cartilage, which was normal, though somewhat brownish, but a deep pink staining of the synovia and soft tissues took place. In one case, the menisci stained slightly. When the dye was poured over the opened joint, the cartilage stained relatively uniformly but not deeply. The menisci stained well.

Alcoholic and watery eosin stain cartilage alike.

Through the arthroscope, it is noted that the joint space is colored a fluorescent green, while the cartilage and soft tissues stain pink. Eroded areas are well seen. There is no metachromasia.

Eosin was injected into ten joints, alcoholic eosin into five and watery eosin into five. Eosin may be said to possess powers of selective staining, with particular predilection for eroded areas in cartilage and less for degenerated areas.

Hematoxylin.—Hematoxylin was injected into three or four joints. The staining of cartilage is slight. instantaneous and superficial. and not washable. uniform. metachromatic or selective. though degenerated areas

seemed to take the stain well. Staining is never widespread. In one case, the hematoxylin was injected into the knee joint of a deeply jaundiced man (carcinoma of the pancreas). The stain was slight, and, on exposure of the cartilage to air, after the joint was opened, the blue of the hematoxylin mixed itself with the yellow-green of the jaundiced cartilage, producing a weird color effect.

If hematoxylin is poured over the opened joint, it does not stain the cartilage uniformly, but a bit more diffusely than in the closed joint. The combination of eosin and hematoxylin has been already noted.

The semilunar cartilages stain on their superior and inferior surfaces, though not diffusely. The free edge may stain a bit more deeply. The synovial membrane and the crucial ligaments stain only slightly.

Acid hematoxylin (a brown solution) stains cartilage neither in the closed joint nor in the open joint.

Hematoxylin, as indicated in these few experiments, seems to be a weak dye, with no particular power of selectivity.

Methylene Blue.—Methylene blue was injected into five joints, the alcoholic solution into three and the watery one into two. Two of the joints showed absolutely normal cartilage. Staining of cartilage, with either the alcoholic or the watery solutions, is instantaneous, very diffuse, superficial, nonselective and not washed away by a strong stream of water, both in normal and in arthritic joints. Cartilage stains diffusely and deeply blue, without regard to the nature of the cartilage, though certain areas in cartilage do not stain at times. The synovial membrane and its villi are well stained. The menisci stain completely both on their two surfaces and on their free edge. The crucial ligaments stain particularly well. The quadriceps bursa stains a deep blue.

Metachromasia of soft tissues and of cartilage is definitely noted here, the color gamut being from blue to blue purple to red purple. This altered staining disappears on exposure to air.

In one case, only the inner half of the joint (an inner puncture being used) was stained, fat apparently blocking the spread of the dye to the outer half of the joint.

Pouring the dye over the opened joint does not increase the intensity of stain or alter its type or extent.

Alcoholic methylene blue was injected into a knee joint of each of two rabbits, with results identical to the foregoing ones.

Through the arthroscope, after the dye has been washed out, the stained areas are clearly visible. The joint space is a peculiar blue brown.

Sudan III.—This dye was used in two cases. Once, it was injected into the normal shoulder joint of a young man, with no staining of cartilage or synovia. In the second case, it was poured over the opened

knee joint of a man 34 years old, dead of tuberculosis; no immediate staining resulted. After a few minutes' exposure, fat was noted to be stained an orange yellow, and the fibrillar cartilage of the patella a slight yellow.

Alcoholic Methyl Violet.—This dye gave a strong, diffuse, blue-violet staining of all structures within the knee joint in the two cases in which it was used. Cartilage stains blue-violet, with possibly a slight predilection for degenerated areas. Synovia and its villi stain deeply blue. The semilunar cartilages stain diffusely well. The crucial ligaments stain well also. Metachromasia was noted in one case.

The stain deepens on exposure to air. If the dye is poured over the opened joint, the type or the extent of the staining is not changed. The staining of cartilage is superficial and instantaneous.

Lithium Carmine.—This dye, when injected into the knee joint (one case), stains instantaneously, very superficially and with an apparent predilection for diseased areas in cartilage, i.e., selectivity in staining. When it is poured over the opened knee joint, it does not stain cartilage further.

Neutral Red.—This dye was used in three knee joints. The stain is dark red, instantaneous, superficial and not washable; it is definitely selective for eroded areas in cartilage, and possibly less so for degenerative, fibrillar areas. Where the cartilage is fibrillar, the stain may then be diffuse. In one case, in an area of apparently normal cartilage, a deep staining took place; on cutting into the cartilage, a brown, degenerated area was observed beneath the surface. Possibly, then, this dye has the power to reveal early areas of degeneration in cartilage, not as yet visible to the eye. The menisci of the knee joint, the crucial ligaments and the synovia with its villi also stain a little.

When the dye is poured over the opened joint, one also notes that this dye has a definite predilection and selectivity for eroded and diseased areas in cartilage, though the staining here is a bit more diffuse.

A section of stained cartilage was examined by frozen section. It was noted that the stain was very superficial and confined to the upper cell layers, and stained the capsule, cells and intercellular substance equally well. The space between the capsule and cell, however, did not stain.

Bismarck Brown.—This dye was used in one case, giving a slight brown tinge to the cartilage. Poured over the cartilage of the opened joint, it did not stain.

Two Per Cent Gentian Violet.—This dye (used in one knee joint) stains irregularly, diffusely, instantaneously, superficially and without powers of selectivity. The staining is deep violet blue. All structures

stain almost equally well (cartilage, crucial ligaments, menisci, synovia). When the dye is poured over the opened joint, similar staining results. The staining capacities of the dye were examined through the arthroscope.

Concentrated Orange Solution.—The dye was injected into one hip joint with no resultant staining. The dye poured over the opened joint stained cartilage and synovial membrane slightly yellowish orange.

Toluidine Blue.—The dye was injected into one knee joint. Certain areas in cartilage, possibly degenerated, stained blue and also metachromatically. The stain is instantaneous, superficial, not washable and possibly selectively weak in staining. Menisci, crucial ligaments and the inner surface of the synovia stained a little. The metachromasia (blue to red purple) faded on opening the joint. The dye poured over the opened joint causes a slightly increased bluish staining of cartilage.

Concentrated Alcoholic Solution of Thionine.—When this dye is spilled over an opened joint, it stains cartilage and synovia very slightly, the stain deepening on standing.

Alum Carmine.—When this dye is injected into the closed knee joint, it does not stain; when it is poured over the opened joint, it stains cartilage and synovia slightly, superficially and unevenly.

Litmus Solution.—To test the action of indicators in their ability to stain joint cartilage, a watery solution of blue litmus (alkaline) was injected into the knee joint of one patient. It is to be noted that the water of Dresden is alkaline. No accurate chemical test of alkalinity was made. The color of the solution did not change, which indicates that the p_H of the joint fluid after death was still roughly alkaline. There was a slight bluish, superficial, easily washable staining of the joint cartilage. When litmus was poured over the opened joint, there was only a slight staining of cartilage, easily washed away by a stream of water. The color of the litmus did not change.

Bile.—A weak solution of bile was injected into the knee joint in one case with no resultant staining. No staining occurred when the bile was poured over the opened knee joint. The solution was evidently too weak to stain. It was noted that a drop of concentrated bile, poured accidentally from an opened gallbladder over the patella, stained it a green yellow, the stain being deep in color and not washed away by a stream of water.

COMMENT

It can then safely be concluded that there are dyes that stain cartilage slightly or not at all, dyes that are diffuse in action, and dyes that are selective. The term "selectivity of action" means that these

dyes stain only eroded or degenerated areas in cartilage and leave normal cartilage unstained.

The course then is clear—to find those dyes that are selective and harmless. A series of experiments should be undertaken to determine the nature of dyes that stain selectively, the amount of dye necessary for use in a joint, the reaction of the joint to the dye, the absorption of the dye, the ability or inability of the dye to cause an experimental or clinical arthritis, the physical, chemical and biologic reasons that underlie selectivity, with special reference to the chemical nature of the dye and the biologic properties of the diseased area. Once this is determined by patient research, it will be possible to utilize these new facts in arthroscopy. Stained areas are clearly outlined through the arthroscope, much better than unstained areas, especially areas of erosion, which are difficult to visualize.

It is possible that the staining reactions described may not occur in living cartilage in the living person. The few animal experiments performed by me indicate this premise to be wrong. Whether one can call the intra-articular injection of dyes for the purpose of staining cartilage vital staining is questionable; it surely cannot be so called in the usually accepted sense of the term. What relation changes in the alkalinity of the synovial fluid bear to the staining of cartilage is not as yet known. Even after death, it appears that the synovial fluid, remains alkaline. and rarely in life does it reach a p_H lower than 7. It may be probable that the sometimes oily fluid exerts a protective effect against cartilage staining. Why there should be a difference between the staining powers of cartilage in the opened and in the closed joint is still conjectural. It is important to find a blue dye that stains selectively, since a red dye gives poor color contrast. especially in hyperemic or other inflammatory conditions of the joints.

CONCLUSION

Of the several dyes examined, eosin. neutral red and lithium carmine seem to stain diseased areas in cartilage selectively. This selective staining is of definite value in arthroscopy, delimiting, as it does, areas of disease in color, thus rendering visualization easy. The work presented here is only the most preliminary of studies.

FORTY-NINTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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This Report of Progress is based on a review of 195 articles selected from 359 articles dealing with orthopedic surgery appearing in the medical literature approximately between April 5 and July 30, 1932. A few selected articles of an earlier date are included. Only those papers that seemed to represent progress have been chosen for review.

CONGENITAL DEFORMITIES

Open Reduction of Congenital Dislocation of the Hip.—Howorth and Smith [1] reported observations in 72 cases of congenital dislocation of the hip in which the patients were treated by open operation from January, 1920, to July, 1929. In 26 cases the dislocation was bilateral. The average age was 4 years and 8 months. In the treatment of 46 of the 82 hips, previous attempts at closed reduction had failed.

The operations used were as follows: (1) simple reduction, 54 per cent; (2) gouging of the acetabulum followed by reduction, 20 per cent; (3) shelf operation, 11 per cent. In two hips it was necessary to reshape the femoral head. The anatomic and functional end-results were summarized; reduction was maintained in 66 per cent. Eighteen months after the first operations subluxation occurred in 31 per cent. Dislocation recurred in only 8 per cent. A good functional result was gained in 67 per cent.

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1. Howorth, M. B., and Smith, H. W.: J. Bone & Joint Surg. **14:**299, 1932.

Kidner[2] reviewed briefly the controversy between the schools advocating open and closed reduction of congenital dislocated hips. He has become convinced that open reduction gives the better result except in the rare young patient in whom the gentlest manipulation results in reduction.

He stated that the great obstacle to reduction, as shown on the operating table, was a redundant adherent capsule and not bony, cartilaginous or muscular changes as many workers had assumed. He found that little force was necessary usually to obtain reduction if the capsule was adequately freed. His operative approach consisted in an anterior incision extending downward from the anterior superior spine, retracting the sartorius medially and the tensor fascia and gluteus medius laterally. The capsule was reflected downward from the ilium as far as the superior border of the acetabulum. The capsule was then incised longitudinally, and the head of the femur was replaced in the acetabulum, which was enlarged if necessary. The redundant capsule was used as a reenforcing ligament. The leg was immobilized in abduction and internal rotation for from eight to twelve weeks. After physical therapy, walking was permitted. Kidner stated that inversion of the neck usually disappeared after reduction and in any case did not affect the end-result. He stated that in twenty-five cases in which operations were performed there was one postoperative death. In the others good results were obtained. There were no recurrences of the dislocation.

[ED. NOTE.—Open operation in congenital dislocation of the hip is coming into greater favor, particularly in the older or more difficult cases, because of the pathologic changes that often prevent reduction by manipulation. The end-results tabulated here, while on a small number of cases, are encouraging.]

DISTURBANCES IN BONE GROWTH

Osteitis Deformans.—Belden and Bernheim[3] made a study of 26 patients with osteitis deformans and as a result concluded that Paget's disease was a metabolic unbalance governed by the ductless glands. They believed that the apparent overaction of the parathyroid glands could best be controlled by a proper dietary and medical regimen. This was as follows: viosterol. 10 drops three times a day; tomato juice, 6 ounces (178 cc.) three times a day. and calcium lactate. 40 grains (2.6 Gm.) twice a day. Improvement was observed in all of the patients under this treatment.

2. Kidner, F. C.: South. M. J. **25**:350, 1932.

3. Belden, W. W., and Bernheim, A. R.: Radiology **18**:324, 1932.

Roentgenography of the Bones in Gaucher's Disease.—Reiss and Kato [4] studied 3 cases of Gaucher's disease in regard to the changes in the bones. The most constant and typical changes were observed in the lower end of the femur, which usually had a moth-eaten, punched-out appearance. There was an osteoporosis throughout the shaft. Pathologic fracture without bony displacement was common. The other long bones were frequently involved. Compression of the vertebrae was observed without a disappearance of the intervertebral disk, although the disks might be invaded extensively by the disease.

The Growth of Bone.—Jansen,[5] in the Lady Jones Memorial Lecture delivered at Liverpool on Feb. 17, 1931, traced the development of certain concepts in regard to the formation and growth of bone. He showed how both excessive and subnormal functional pressure led to the absorption of lime salts from bone, and that an enhanced deposition of lime salts occurred somewhere between these two extremes. He believed that in exercise the bones were as well developed as the muscles. Two aspects of the increased vulnerability of the rapidly growing cells of bone were given: (1) Injurious agents of all kinds might cause feebleness of growth. (2) The signs of feebleness of growth were given in three degrees: (*a*) The slight degree was characterized only by muscular weakness, weak feet, a prominent abdomen, round shoulders and blue hands and feet; there was usually an overgrowth in adolescence. (*b*) The moderate degree was represented by the knock-kneed child, neither too tall nor too short. (*c*) The severe degree was characterized by severe muscular weakness; all of the cartilages of growth were affected, and the entire skeleton lagged behind the normal in growth. The severe form of enfeeblement of growth was observed in the first few years of life. Enfeebled bone substance showed two characteristics: increased fatigability and increased irritability. By studying the quantitative changes in growth in the locomotor apparatus, evidence of a feeble constitution might be obtained. The discovery and removal of the causes of such enfeeblement of growth would remove much disease and crippling of the human race.

[ED. NOTE.—Jansen's views on the various factors influencing the growth of bone are thought provoking and merit consideration and for this reason they are worth while even if we are unable to agree with all of his conclusions.]

NEOPLASMS

Fibrosarcoma of Bone.—Geschickter [6] stated that the osteogenic portions of the bone do not give rise to sarcoma of the true spindle cell

4. Reiss, O., and Kato, K.: Gaucher's Disease: Clinical Study, with Special Reference to Roentgenography of Bones, Am. J. Dis. Child. 43:365 (Feb.) 1932.

5. Jansen, M.: Surg., Gynec. & Obst. 54:175, 1932.

6. Geschickter, C. F.: So-Called Fibrosarcoma of Bone: Bone Involvement by Sarcoma of the Neighboring Soft Parts, Arch. Surg. 24:231 (Feb.) 1932.

type. Connective tissue tumors in bone arise from fibroblasts with a tendency to bone formation or from precartilaginous connective tissue destined to form bone via the intracartilaginous route. His study of thirty-one cases showed that the histologic composition of the new growth was a more reliable index of its clinical and pathologic behavior than its anatomic location or apparent relationship to bone. Fibrospindle cell tumors should be studied in regard to the transition from oat cell to spindle cell to fibrospindle cell to adult fibroblasts. The more primitive the connective tissue cell, the more malignant was the tumor. In the undifferentiated oat cell type, neither excision nor roentgen therapy offered more than temporary relief. In neurogenic tumors involving bone, a similar microscopic gradation could be made. The more malignant the tumor, the greater was the number of large pleomorphic nuclei and the more closely packed the spindle cells. The prognosis was extremely bad, death usually occurring in two years. The author mentioned that bone was sometimes invaded by connective tissue tumors arising from outside the bone which gave a similar clinical picture, such as angiomas, myosarcomas and lipomas. When the fibrosarcoma was not of the oat cell type, an attempt to eradicate the disease locally was justifiable. In the oat cell type, immediate amputation was indicated. Amputation was the treatment of choice in neurogenic sarcoma involving the bone. For angiomas, local excision followed by irradiation seemed the best treatment. Local excision was advocated for lipomas and amputation for myosarcomas.

THE BACK

Backache; Anatomic Consideration.—Willis [7] reported his studies on the anatomy of many spinal columns at Western Reserve University. He was particularly interested in the anomalous developments, such as spina bifida occulta, asymmetric sacralization and the "separate neural arch," a defect in one or both laminae occurring between the superior and inferior articular processes of the lumbar vertebrae, most often the latter. The relationship of this last anomaly to spondylolisthesis was, as pointed out by the author, well known. Willis found the defect present in 79 instances in a study of 1,520 skeletons, an incidence of 5.9 per cent.

Spondylolisthesis.—Meyerding [8] reviewed the findings in 207 cases of spondylolisthesis; 148 were in male patients and 59 in female patients. The condition was found to be due to instability of the lumbosacral articulation and to congenital defects in the lumbosacral region. A number of patients had spondylolisthesis without symptoms. The

7. Willis, T. A.: J. Bone & Joint Surg. **14**:267, 1932.

8. Meyerding, H. W.: Surg., Gynec. & Obst. **54**:371, 1932.

chief symptom was backache, with or without radiating pain. Prominence of the sacrum and a shortened torso were commonly observed. Neurologic disturbances were rare. X-ray pictures, particularly lateral ones, helped greatly in the diagnosis. While spinal support often relieved the symptoms, the author advised fusion of the sacrum to the lower lumbar spine.

Typhoid Spine.—Wang and Miltner [9] reported 2 cases of typhoid spine, 1 of which also presented a destructive arthritis of the sacro-iliac joint. There was complete recovery in both cases, with bony ankylosis of the spines in the involved areas. The treatment used was prolonged recumbency followed by a spinal support. There was bacteriologic verification of the diagnosis in both cases.

Gibbus Resulting from Tetanus.—Ciaccia [10] collected cases from the literature, and added 2 of his own in which gibbus developed following tetanus. All of the lesions were dorsal in location excepting 2 in the lumbar region. They were characterized by an absence of destruction of the intervertebral disks, an absence of abscess formation and partial collapse of from one to three vertebral bodies. Various etiologic factors were discussed at length; chief among these was the spontaneous vertebral collapse in the presence of maintained muscular spasm. In 1 case Ciaccia fused the spine, and in the other he obtained a satisfactory result by conservative therapy.

SUPPURATIVE ARTHRITIS

Suppurative Arthritis of the Hip.—From a study of 18 septic hips in 17 children, Caldwell [11] concluded that it was important to establish the diagnosis of such a condition early and to determine, if possible, whether the infection was primarily an osteomyelitis of the femoral neck or whether it originated from the synovial lining of the joint. In all of the 17 cases the infection was of hematogenic origin. To wait for roentgen evidence in the presence of sepsis was often disastrous, because this rarely occurred before two weeks had elapsed. He favored early aspiration of the joint as a means of establishing the diagnosis. Twelve hips were drained by anterior incisions, 2 posteriorly and 4 by incisions over the inner side of the thigh, where abscesses were pointing. Postoperative traction in abduction was considered most essential to prevent dislocation. In cases in which there was a primary osteomyelitis or epiphysitis, ankylosis of the joint was apt to result. Frequent x-ray pictures during convalescent treatment were desirable to determine whether there was osseous involvement.

9. Wang, L. K., and Miltner, L. J.: Chinese M. J. **46**:1, 1932.

10. Ciaccia, S.: Chir. d. org. di movimento **16**:531, 1931.

11. Caldwell, G. A.: Acute Suppurative Conditions of the Hip Joint, J. A. M. A. **98**:37 (Jan. 2) 1932.

TUBERCULOSIS

Operative Treatment of Tuberculosis of the Joints.—Henderson [12] reviewed the present trends in the treatment of tuberculosis of the bones and joints. He stated that conservative treatment has its greatest field of usefulness in children, while operative treatment aiming to ankylose the diseased joints and to eradicate the disease is the treatment of choice in adults. It is important to select the patients for operation carefully, since the results in America are still poor, owing in large part to the unwillingness of patients to continue treatment sufficiently long. Each patient must be studied before the type of treatment can be decided. In general, patients in whom operative treatment is advisable should be beyond the age of puberty, free from active pulmonary tuberculosis and from tuberculosis of the genito-urinary tract and also in good general health. The author advised against extensive operative procedures in the presence of draining sinuses. In a series of more than 600 cases, the operative mortality was less than 1 per cent.

Liver Meal in the Treatment of Amyloidosis in Surgical Tuberculosis.—Whitbeck [13] treated 7 patients with amyloid disease following tuberculosis of the bones and joints with liver extract. Powdered whole liver was used and given in doses of 1 drachm (3.9 Gm.) three times daily. Two patients died, 1 from an intercurrent infection and the other from cardiac failure. The other 5 showed benefit three months after therapy had been instituted, and thirteen months later there was distinct improvement, as evidenced by a diminution in the size of the liver and spleen, less anemia, less ascites and improvement in the general state of nutrition. However, in each case the Congo red test was positive at the end of eighteen months, indicating that sufficient lardaceous material was present in the organs to absorb the dye and to remove it completely from the blood.

POLIOMYELITIS

Production of Antiviral Substances.—Howitt, [14] by the injection of poliomyelitis virus into 2 sheep and a goat over a period of years, was able to produce antiviral substances capable of protecting monkeys against infection. The author demonstrated also by a higher percentage of recoveries that the intramuscular route was preferable to the combined intravenous and intrathecal routes in giving convalescent serum to monkeys in the preparalytic stage of poliomyelitis.

Convalescent Serum in Preparalytic Poliomyelitis.—In a fairly well controlled group of patients in the preparalytic stage of poliomyelitis in

12. Henderson, M. S.: Minnesota Med. **15**:141, 1932.

13. Whitbeck, B. H.: J. Bone & Joint Surg. **14**:85, 1932.

14. Howitt, B. F.: Proc. Soc. Exper. Biol. & Med. **29**:118, 1931.

southern New England in 1931, Kramer and his co-workers [15] made a careful study of the therapeutic effect of human convalescent poliomyelitic serum given by the combined intraspinous and intravenous routes. The authors were unable to obtain conclusive evidence that the convalescent serum was of value, or, on the other hand, that it was valueless.

Abortive Poliomyelitis.—Paul and his associates [16] reported the results of an epidemiologic study of poliomyelitis with particular reference to cases of "abortive" poliomyelitis. By "abortive" poliomyelitis was meant a minor illness showing more or less regular characteristics and occurring during an epidemic of poliomyelitis. The symptomatology of these minor illnesses was not specific, but was essentially that of an acute infection of short duration, symptoms of fever, sore throat, headache and vomiting dominating the picture. A survey of 222 families, in each of which 1 or more cases of poliomyelitis developed, showed that in from 32 to 39 per cent of the other children, i. e., those not coming down with poliomyelitis, minor illness developed coincidentally with the onset of the known cases. In 60 control families studied, it was found that only 9 per cent of the children had minor illnesses during the time of the epidemic. It seemed reasonable to suppose that at least some of the minor illnesses were related to orthodox poliomyelitis. Only if it could be shown that a child became immune subsequent to the development of a minor illness could it be assumed that he had passed through an attack of the disease. This proof awaited further knowledge of the nature of immunity and of the means of measuring it.

Poliomyelitis in California.—Meals and Bower [17] reviewed the 1930 epidemic of poliomyelitis in southern California; 350 cases were studied. Spread by "healthy carriers" was frequently observed. The patients were seen, on the average, on the fourth day of the illness. In 11.7 per cent of the cases, paralysis was found on the first examination. In 12.86 per cent, the spinal fluids were negative, but the patients showed characteristic neurologic findings. Twenty-two per cent were negative neurologically, but showed the usual changes in the spinal fluid. Treatment was almost wholly with pooled convalescent serum plus rest and immobilization, with dietetic and eliminative measures. Serum was given, either 15 cc. intrathecally or 30 cc. intramuscularly or intravenously; the mode of administration depended on the severity and the advancement of the disease. The authors preferred the intravenous

15. Kramer, S. D.; Aycock, W. L.; Solomon, C. I., and Thenebe, C. L.: New England J. Med. **206**:432, 1932.

16. Paul, J. R.; Salinger, R., and Trask, J. D.: "Abortive" Poliomyelitis, J. A. M. A. **98**:2262 (June 25) 1932.

17. Meals, R. W., and Bower, A. G.: J. Lab. & Clin. Med. **17**:409, 1932.

or intramuscular administration of serum when there were no phenomena of the central nervous system. In 82 per cent of the cases, the fever abated and the subjective symptoms subsided after the intracisternal injection of serum. In this series there were 60.9 per cent complete recoveries. In 25.66 per cent there was mild residual paralysis, and 10.28 per cent showed more extensive paralyses. The mortality was 3.16 per cent. In the entire country the death rate during this epidemic was 7 per cent.

[ED. NOTE.—The therapeutic effect of convalescent serum in the treatment of preparalytic poliomyelitis is still sub judice. The most carefully controlled observations, although small in number, throw a doubt on the usefulness of the serum. Its use, however, should be encouraged until the matter is settled.]

ARTHRITIS

Hemophilic Arthritis.—Key [18] reported a thorough study of a case of chronic hemophilic arthritis of the knee in which the patient was operated on because of a mistaken diagnosis. Macroscopic and microscopic studies were reported. Key divided hemophilic joints into two types: the acute hemarthrosis and the chronic arthritis. The first type represented the first or early attacks in which the picture was one of intrasynovial hemorrhage, varying in the severity of the symptoms according to the amount of hemorrhage. The second type, a joint into which there had been numerous hemorrhages over a period of years, showed a rather characteristic group of signs and symptoms. Grossly and clinically, this joint simulated almost any of the various types of chronic arthritic lesions. When the lesion was opened, the appearance was characteristic—a thickened, deeply pigmented synovial membrane with a fibrous subsynovial tissue, maplike destruction of the articular cartilage, replaced by either fibrous tissue or unorganized blood clot, and atrophic irregular subchondral osseous structure. A flexion deformity of the joint was frequently seen. Operative intervention was contraindicated; conservative therapy alone should be used. An excellent study of the various types of joints was given, as well as a review of the scant literature on these lesions.

Syphilitic Arthritis with Effusion.—Among 112 cases of acute and chronic arthritis with effusion, Kling [19] found that 9 (8.1 per cent) were due to syphilis. All cases showed late manifestations of the disease. Over half of the cases were due to congenital syphilis. Seven showed involvement of the synovial membrane only; 1 patient had a juxta-articular gumma; another had osteochondritis and periostitis.

18. Key, J. A.: Ann. Surg. **95**:198, 1932.
19. Kling, D. H.: Am. J. M. Sc. **183**:538, 1932.

Kling based the diagnosis on (1) the presence of syphilis as shown by the Wassermann reaction of the blood and by other syphilitic lesions, i. e., keratitis and gumma, and (2) examination of the affected joint. He found that complete examination of the fluid of the joint was most important, particularly the Wassermann reaction. He found that a therapeutic test was of value in doubtful cases, always proving of benefit if the diagnosis was correct.

CIRCULATORY DISTURBANCES

Raynaud's Disease.—Allen and Brown [20] studied 150 cases of Raynaud's disease in order to determine the minimal requisites for diagnosis. They found that the symptoms described by Raynaud were necessary for a diagnosis. These were: gangrene or trophic disturbances limited almost wholly to the skin, symmetrical or bilateral involvement, absence of evidence of any occlusive lesions of the peripheral arteries and intermittent attacks.

Deep Ligation of the Vein for Gangrene.—Pearse [21] reported the results of deep ligation of the vein in 20 cases of diabetic and arteriosclerotic gangrene. Thirty-one additional cases from the literature were reviewed. Ligation of the external iliac vein, the femoral vein or the popliteal vein was done. Of 20 patients so treated, the results in 8 were successful, the results in 8 were failures, and 4 patients died within a year without amputation. The cases were divided into 3 classes: (1) cases in which amputation of the leg should be done; (2) those in which amputation should not be done, and (3) borderline cases. The beneficial results from ligation of the vein were warmth, diminution of pain and objective changes in the limb. Edema rarely occurred. Additional factors in the treatment of such limbs were enumerated in a discussion of the preoperative and the postoperative treatment.

20. Allen, E. V., and Brown, G. E.: Am. J. M. Sc. **183**:187, 1932.

21. Pearse, H. E.: The Use of Vein Ligation in the Treatment of Arteriosclerotic and Diabetic Gangrene, J. A. M. A. **98**:866 (March 12) 1932.

(To be Concluded)

ACUTE OSTEOMYELITIS OF THE VERTEBRAE

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Acute osteomyelitis of the vertebrae constitutes a clinical entity of interest and importance to both the internist and the surgeon. The disease consists of an acute suppurative spondylitis generally consequent on metastatic infection of the vertebrae at the time of a previous bacteremia, occasionally the result of the involvement of the vertebrae by a local inflammation that has spread by direct extension. The malady is serious, is often not recognized promptly and is attended with a considerable mortality. The American literature has paid this subject scant attention. The following sixteen cases, proved by operation or necropsy, have occurred in the Mount Sinai Hospital chiefly during the past seven years and are presented to serve as a basis for the analysis of the disease and its clinical aspects. The aim of this study is clinical. For statistical and theoretical discussions of the subject, the reader is referred to Volkman,[1] Wilensky[2] and Borchers.[3]

CLINICAL CONSIDERATIONS

In general, the history, mode of onset and generic symptomatology of all the cases had many features in common. However, for clinical purposes, it has been possible to subdivide the series into four groups according to the nature of the presenting clinical condition. The latter was usually a complication, e. g., epidural abscess, and often dominated the clinical scene.

History.—It is most important to elicit the history of a preexisting lesion which may have been the focus for a bacteremia. In contrast to osteomyelitis of the long bones, to which the young are so prone and which is so often cryptogenetic, the presumable portals of entry were established in fifteen of the sixteen cases. These included boils and carbuncles, previous chronic osteomyelitis, pneumonia, cellulitis of the

1. Volkman, J.: Ueber die primäre akute und subakute Osteomyelitis purulenta der Wirbel, Deutsche Ztschr. f. Chir. **132**:445 (Jan.) 1915.

2. Wilensky, A. O.: Osteomyelitis of Vertebrae, Ann. Surg. **89**:561 (April) 1929; 731 (May) 1929.

3. Borchers, G.: Ueber die primäre akute und subakute Osteomyelitis purulenta der Wirbel, Arch. f. klin. Chir. **158**:168 (Feb.) 1930.

arm, phlebitis of the hepatic vein radicles subsequent to cholangeitic abscess of the liver, acute bacterial endocarditis of the aortic and mitral valves, cystitis with purulent prostatitis, mastoiditis with mastoidectomy, lateral sinus thrombosis, purulent bronchitis in cachexia (phlebitis of the smaller radicles of the pulmonary vein?) and a secondarily infected hematoma. Typhoid fever, paronychia, alveolar abscess, pharyngitis and mastitis may also be sources of bacteremia with metastatic osteomyelitis.[1] A history of true rigor may be obtained, and is of great significance even though it may have occurred many months before. Trauma played no appreciable rôle in this series of cases.

Mode of Onset.—As well as could be determined, the shortest time in which objective evidence of a local pathologic process developed was ten days (case 2). In all the other cases, at least two weeks were necessary. Generally, a little local pain or rigidity was complained of; this gradually became more severe until there was complementary evidence of local disease. In no case was there sudden onset with severe local symptoms and signs pointing to the underlying processes. *Pari passu* with the aggravation of the local condition was the intensification of the systemic indications of the infection.

Generic Characteristics.—In contrast to the osteomyelitis of the long bones, only two of these cases occurred in children. The patients were all febrile and apparently suffering from an infection, with the customary manifestations of fever, tachycardia, leukocytosis, albuminuria, etc. These observations show the necessity for careful investigation when the process is not superficial and therefore obvious. None of the cases presented the appearance of rapidly fatal overwhelming infection, with signs only of generalized intoxication without localization, which is occasionally seen in osteomyelitis of the long bones. The difference may be due to the relatively small amount of marrow infected, in contrast to the amount involved in disease of the long bones.

The following local characteristics may be common to osteomyelitis of the spine, no matter where situated:

1. There is pain, especially on motion. The aggravation of the pain on motion may be due to the spasm of the contiguous musculature or to pressure on a diseased intervertebral disk. Pain on jolting is often absent and is less prominent than in tuberculous spondylitis.[1]

2. Local tenderness may or may not be present over the spinous processes. It is less apt to be present when only the bodies of the vertebrae are diseased. In two cases pain was maximal over normal vertebrae. In case 10, clinically, tenderness had been elicited over the spinous processes of the second and third sacral vertebrae; however, at necropsy, the osteomyelitic foci were found in the second and third lumbar vertebrae.

3. Signs of local inflammation generally indicate perforation and are most commonly present when the laminae or processes are affected, but may be present in exclusive involvement of the vertebral bodies.

4. There is a grating sensation on palpation, owing to sequestration of a spinous process.[1]

5. Local deformity with actual gibbus may occur, owing to the collapse of the diseased vertebrae, as in case 13. Generally, there is only transient deformity, due perhaps to muscle spasm which disappears with the subsidence of inflammation.[1]

The cases may be divided into the following groups:

Group I. The most frequent clinical picture presented is that of abscess formation. This may occur anywhere along the spine. Although the pathologic process is everywhere essentially the same, the difference in the location of the site involved causes a variety of clinical pictures. In the order of frequency these are as follows:

A. The abscess generally presents in the back, near the vertebral column. The skin over the suppurating area most often reveals no local etiologic lesion (when the process is metastatic in origin). There may be no signs or symptoms of underlying bony disease. In this series, ten days was the shortest period of time for the formation of an abscess large enough to be recognized. At operation bare bone is felt at the base of the abscess cavity. This establishes the osteomyelitic origin of the abscess.

B. The next most frequent situation for the abscess is the region of the psoas magnus muscle. A tremendous collection of pus may be present here and yet not cause a swelling conspicuous enough to be detected by careful physical examination. Its existence may have to be inferred from the presence of tender enlarged inguinal lymph nodes associated with homolateral psoas spasm. When a tuberculous abscess of the spine gravitates along the psoas muscle down to the inguinal region, caseating inguinal adenopathy occasionally develops in a similar fashion, but the swelling created is cold, indolent and generally not tender. Because of the involvement of lumbar nerve roots by the inflammatory process, there may be abdominal distention, pain and rigidity, so that one may be inclined to infer the existence of an acute surgical inflammation within the peritoneal cavity ("acute abdomen"). The presence of costo-vertebral tenderness, with a local mass or spasm of the lumbar muscles and purulent urine, may lead to the erroneous diagnosis of perinephritic abscess, secondary to a perforated cortical abscess of the kidney. Since this is frequently a concomitant metastatic lesion, the diagnosis may be established with certainty only at operation.

C. An apparently idiopathic abscess may present in the buttock. At operation bare bone may not be felt at the base of the abscess

cavity. In such a case one must investigate the lumbar and sacral vertebrae for the presence of an osteomyelitic focus. A collection of pus arising from these vertebrae may gravitate down along the tissue planes, pass through the major sciatic foramen and present in the buttock. It may also pass over the crest of the ilium and present in the buttock. It is because of this devious route that bare bone is not encountered at operation. The collection of pus may pass through the minor sciatic foramen and present beside the anus. This may be the explanation for a persistently draining ischiorectal abscess.

D. The mediastinum may also be the seat of abscess formation. The patient may complain of pain in the chest or abdomen, a pleuritic friction rub may be heard, and later there may be present an area of dulness with diminution of breath sounds. Constant dry cough and hiccup may occur. The diagnosis of mediastinal abscess is made by (1) a history of a focus capable of giving rise to a bacteremia, (2) localized tenderness over the spinous processes of the thoracic vertebrae and (3) roentgenographic evidence of widening of the mediastinum, like that produced by mediastinal collections of fluid.

Group II. The second most frequent clinical group is that in which the patients present a variety of complaints referable to the nervous system. There may be paresis or paralysis of a limb, sphincteric disturbances, abnormalities in the reflexes, impairment of sensory perception or tenderness along the peripheral nerves. Because of the presence of an infection elsewhere in the body and findings that simulate those of myelitis or peripheral neuritis, an erroneous diagnosis of "toxic myelitis" or "toxic neuritis" is often made. The signs and symptoms are generally due to involvement of the nerve roots by the inflammatory exudate or to compression of the spinal cord, which is consequent on pachymeningitis, epidural abscess, etc., the result of perforation of the osteomyelitic focus. The latter must be suspected when a patient with a history of an inflammatory focus capable of giving rise to a bacteremia shows signs and symptoms referable to disease of the spinal cord. Of great diagnostic value are tenderness over the spinous processes, signs of a level lesion, evidences of spinal subarachnoid block and pleocytosis in the cerebrospinal fluid. This group of related conditions in a patient suffering from an infection is most suggestive of perforation of an osteomyelitis of the vertebrae.

Group III. In this group may be classed those patients who present only pain in the back and fever. No other findings may be elicited despite elaborate efforts to determine the cause of the pain. Symptomatic measures fail to give relief. Roentgenographic examination of the painful segments of the spine may yield negative results despite months of suppuration. Diagnosis is most difficult in these cases and may be established only by operation. When the general clinical picture

indicates the existence of infection and there is a history of previous bacteremia, an exploratory operation may have to be performed, especially when the painful area is tender. It may be fatal to postpone operation until one has the confirmatory evidence of a complication (spinal meningitis).

Group IV. The fourth group includes those patients who suffer from widespread suppuration consequent on a bacteremia. There are multiple abscesses throughout the viscera, e. g., in the kidneys, spleen and lungs, and, coincidentally, abscesses in the vertebrae. The clinical picture produced is a summation of the signs and symptoms due to the suppurative spondylitis, as described in the first three groups, and those dependent on the nature and location of the coincident metastatic abscesses elsewhere and the complications subsequent to them.

The cases comprising this group are least in importance from a therapeutic standpoint. Even if the bone focus is susceptible to adequate treatment, death occurs because of the already established, generalized, metastatic abscesses. However, in cases in which the osteomyelitic focus is itself the source of a bacteremia, often persistent, adequate local treatment may eradicate the focus and terminate the bacteremia; the metastatic foci may heal completely, and the patient may then recover.

PATHOGENESIS

There are two ways in which the vertebral infection may occur. Most frequently, there is a localized infection which gives rise to a bacteremia; bacteria localize in the vertebrae and cause an osteomyelitis. This mode of development is well illustrated by case 10, in which a pneumococcus type I was recovered from the pus in the infected mastoid process, from the blood stream on the day after operation and from the pus in the mediastinal abscess produced by the vertebral osteomyelitis. This development can be traced in cases 5, 10, 11 and 14. In rare instances there is a local inflammation which spreads and involves the vertebrae by direct extension (case 6).

BACTERIOLOGY

In the literature the following have been described as causative organisms: Staphylococcus aureus and albus, Streptococcus pyogenes. Bacillus typhosus, Micrococcus tetragenus,[1] B. paratyphosus A [4] and B. perfringens.[5] In addition to these there were found in this series Streptococcus viridans, the pneumococcus, types I, III and IV, and the Friedländer bacillus. In view of the variety of organisms that have

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4. Zanboni, G.: Osteomyelite degli archi vertebrali della II-III-IV lombare da paratifo A, Ann. ital. di chir. **5**:499 (May) 1926.

5. Laborde, J. P. A. M.: Étude sur les spondylites staphylococciques de l'adulte, Thèse, Paris, 1926, vol. 39. no. 93.

already been found responsible, it would not be wise to rule out the diagnosis if there should be isolated from a patient suspected of vertebral osteomyelitis an organism (e. g., B. coli) that has hitherto not been described in this condition (see addendum).

In six of the cases, blood cultures were taken, and in each case bacteria were recovered from the blood stream. In four of the cases, the focus causing the bacteremia was distant from the local bone disease, e. g., hepatic vein phlebitis; in one (case 6), it was the local inflammation, and in one other (case 12), it was a phlebitis, complicating a perforation into the soft tissues of the vertebral suppuration. Depending on the nature of the causative focus, the bacteremia was transient (cases 6 and 10) or lasted until the death of the patient (cases 11, 13, 14 and 15).

PATHOLOGY

Anatomically, the cases can be divided into two groups, depending on whether the bodies or the processes of the vertebrae are the sites of the inflammation. In ten cases the bodies were involved; in eight of these there was frank suppuration, often with abscess formation; in one (case 10), the body was merely denuded of periosteum, roughened and tender, and in one other the nature of the corporeal involvement could not be determined. In only three cases was a bony process found to be the seat of the inflammation. In three cases it was not possible to ascertain definitely which portion of the vertebrae was diseased. In the cases in which the process was involved, the inflammation was chiefly superficial, the exposed bone being merely bare and rough. Perforation was earlier when the inflammation occurred in a process, perhaps because of the smaller volume of bone affected.

It is customary to divide vertebral osteomyelitis into cortical, or subperiosteal, and medullary types. To the former belong the cases that present only superficial infection of the bone, which is denuded of periosteum, rough and tender; they occur chiefly in infection of the processes. To the latter belong the cases with frank suppuration and abscess formation; they occur chiefly in infection of the vertebral bodies. If the necrosis is sufficiently extensive, the body may be crushed.

Worthy of mention is a chronic form of the disease described by Radt.[6] In this condition the process may last for many years, with the formation of an ossifying perivertebral granulation tissue which compresses the nerve roots and produces severe, intractable radicular pains.

In cases of bacteremia, it is probable that organisms are carried to many bones besides those which become diseased. Just why certain vertebrae fall a prey to the bacterial invasion is impossible to state. In one case two widely separated vertebrae were infected, while in four

6. Radt, P.: Ueber chronische Osteomyelitis der Wirbelsäule und des Kreuzbeins, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **41**:389 (May) 1929.

cases two annectent vertebrae were diseased. In only two cases can there be implicated a contributory factor, favoring the development of the metastatic process. In one (case 15) there was an old local spondylitis, and in the other (case 16) Hodgkin's infiltrations were present in the vertebral body.

When perforation occurs posteriorly, a superficial abscess forms; it is readily drained, and convalescence is generally uneventful.

Serious complications are usually consequent on perforations that do not come from the processes or laminae and that are not directed posteriorly. Irrespective of the situation of the disease process, the most frequent and most serious complication is that of involvement of the central nervous system. Compression of the spinal cord may be caused by: (*a*) an epidural abscess, secondary to perforation into the epidural space; (*b*) a subdural abscess secondary to epidural infection; secondary to the subdural infection, spinal leptomeningitis may occur and spread to involve the cerebral leptomeninges; (*c*) a pachymeningitis. In a case described by Fraenkel [7] there was a cervical osteomyelitis secondary to infection of a toe; the signs and symptoms of compression of the spinal cord developed; at necropsy the dura mater adjacent to the osteomyelitic focus was found to be thickened and infiltrated with round and plasma cells, among which there were many organisms resembling staphylococci; there was a definite compression of the spinal cord by the thickened dura; there was no epidural or subdural abscess.

Another complication is that of involvement of a major vascular trunk. In case 12, the purulent exudate, surrounding the right common iliac vein, produced a fatal thrombophlebitis. The inflammatory manifestations noted clinically in the right lower extremity were considered the result of retrograde phlebitis, although no substantiation by anatomic examination was undertaken at necropsy. There is a case described by Plenz [8] in which an intercostal vein, secondarily infected by pus from the dorsal vertebrae, was responsible for a bacteremia with metastatic abscesses and a fatal outcome. This thrombophlebitis had caused a swelling of the overlying soft tissues, which were red and tender. This, clinically, was thought to be due to the burrowing of pus from the diseased vertebrae. At operation no pus was found to explain the soft tissue swelling. The thrombophlebitis was neither suspected nor detected and yet was the most important inflammatory process present. A case of fatal erosion of an iliac artery has been reported.[9]

7. Fraenkel, E.: Ueber Spondylitis acuta infectiosa und Rückenmarkserkrankungen, Fortschr. a. d. Geb. d. Röntgenstrahlen **30**:103 (Jan. 15) 1923.

8. Plenz, P. G.: Ueber Osteomyelitis acuta und subacuta der Wirbel, Deutsche med. Wchnschr. **47**:416 (April 14) 1921.

9. Corret, P.; Michon, P., and Reny, F.: Abcès ostéomyélitique vertébral ayant ulcère l'artère iliaque externe chez un ancien blessé de guerre, Rev. méd. de l'est **57**:259 (May 1) 1929.

There are a number of complications recorded which depend on the location of the diseased vertebrae. In the cervical region the following may occur: (1) direct extension of the inflammatory process to the intracranial cavity, generally with fatal cerebral leptomeningitis[5]; (2) involvement of the roots of the phrenic nerve by the inflammatory granulation tissue or pus, with consequent paralysis of the diaphragm; (3) retropharyngeal abscess with respiratory obstruction, and (4) gravitation of the pus into the posterior mediastinum, with possible secondary perforation into a pleural or the pericardial cavity.

In the thoracic region there may occur: (1) perforation into the esophagus and (2) perforation into the mediastinum, with possible secondary perforation into a pleural or the pericardial cavity.

In the lumbar region the following may occur: (1) psoas abscess, the most common complication of lumbar osteomyelitis and already discussed, (2) perforation into the intestine, with consequent purulent diarrhea, and (3) perforation into the urinary tract, with sudden massive pyuria.

Although signs of peritoneal irritation are not infrequent, actual peritonitis is rare. It is most unusual for a psoas abscess to perforate into the peritoneal cavity.

RÔLE OF THE X-RAYS IN DIAGNOSIS

The x-rays were not of great service in demonstrating the presence of osteomyelitis. Only after bone destruction or new bone formation has occurred may one expect roentgenographic change. In eleven of the cases, roentgenograms were taken. In nine of these cases the examination was undertaken before operation or necropsy revealed the underlying pathologic process. In not a single one of these cases did the roentgenologist report evidence of acute osteomyelitis. The plates were either negative for bone disease or revealed nonspecific hypertrophic spondylitis. George and Leonard[10] also noted this tendency to rapid bone formation. The inflammatory processes in these cases varied in duration from at least a week to nine years. In three cases the roentgenograms were positive. In case 1, roentgenograms were taken one month after operation and showed evidence of osteomyelitis. In case 3, x-ray pictures were taken two days after operation and revealed crushing and fusion of three vertebral bodies, the underlying pathologic process being certainly more than two weeks old; the exact duration could not be ascertained. In case 5 roentgenograms were negative the day before operation, but were positive two and a half weeks after operation. Therefore, in a patient with vertebral

10. George, A. W., and Leonard, R. D.: The Vertebrae, Ann. Roentgenol. **8:**70, 1929.

inflammatory disease the roentgenogram may be negative or reveal only evidence of hypertrophic spondylitis, despite the presence of an abscess in the bone, varying in estimated duration from ten days to four months. It is probable that many of the chronic cases (such as case 14 with gibbus formation) would show roentgen changes, but here the diagnosis is no longer in doubt. It may be that with more frequent roentgenographic examinations, the roentgenogram will prove to be of more value (see addendum).

PROGNOSIS

The prognosis is largely dependent on the following factors: A. The presence and nature of an existing complication. Involvement of the spinal cord offers the worst prognosis, and the formation of an abscess presenting in the back and resulting from a posterior perforation, the best prognosis.

B. The localization of the inflammation in the body or a process of a vertebra. In three of the cases presented, death was due indirectly to the local osteomyelitic focus alone, and in each instance the seat of the disease was in the body of the vertebra. In six cases there were concomitant abscesses in various viscera; in five of these cases, the body was the involved portion of the vertebra, while in the sixth the body of one and a process of another vertebra were involved. In three cases the processes were involved and in two others it is probable that the inflammatory process occurred in the processes. In four of these cases, uncomplicated by infection elsewhere, convalescence was uneventful. The fifth patient is in the hospital at present; his progress is satisfactory. In general, therefore, the involvement of the body carries with it a graver prognosis than does involvement of a process of a vertebra.

C. The promptness of the diagnosis and the adequacy of the surgical treatment.

D. The type of bacterium causing the infection. This does not play a considerable rôle; e. g., case 11, due to Streptococcus viridans, was fatal, while in case 10, due to a pneumococcus type I, and case 4, due to Staphylococcus aureus, the patients recovered.

E. The general resistance of the patient. Although it is undoubtedly a factor, it is difficult to evaluate.

TREATMENT

The treatment is surgical. Concerning it I wish to make only the following comment: A. The primary aim is to drain the suppurating area, especially in order to prevent complications due to perforation.

B. The focus in the bone itself must be drained; it is not sufficient to drain the complicating infection, e. g., an epidural abscess. Radical therapy may not be feasible when the patient is acutely ill, but it is nec-

essary for the accomplishment of a complete cure. Patton [11] described a case in point. In a case of thoracic osteomyelitis, there was removed only some necrotic bone, easily encountered, with the drainage of a small amount of pus. However, because of the progression of symptoms and the development of paraplegia, a second and more extensive operation was necessary after an interval of six weeks; on this occasion the diseased spinous processes and laminae and an exudate on the dura were removed, with the resultant disappearance of the paraplegia and a gradual complete cure.

C. The presence of metastatic foci does not contraindicate operation. The osteomyelitis may be the focus of the bacteremia. Cases of bacteremia with metastatic abscesses of the lung are not infrequent, in which, with the removal of the focus of the bacteremia, the abscesses in the lung heal spontaneously.

D. Recovery may occur after operation despite the presence of bacteria and a pleocytosis in the cerebrospinal fluid (case 6). Signs of compression of the spinal cord were present in this case and disappeared after the drainage of a collection of pus exterior to the vertebral column. Acute inflammatory compression of the spinal cord does not necessarily indicate the presence of more than edema of the epidural tissue and does not warrant a nihilistic attitude, even in the presence of evidence indicating an infected cerebrospinal fluid.

The mortality is still considerable. The following estimates are presented:

Makins and Abbott (Ann. Surg. 23:510 [May] 1896)..71.4 per cent
Volkman (1914).....................................41.8 per cent
Borchers (1930).....................................56.3 per cent
Mount Sinai Hospital (1931).........................51   per cent
   (Case 5 excepted)

DIAGNOSIS

From what has been said, one can see how varied the clinical picture may be. The diagnosis must be entertained whenever any patient who has suffered from an infection presents signs and symptoms referable to a vertebral osteomyelitis. A patient who presents a history of a boil and in whom a sudden paraplegia develops must be investigated for epidural abscess. An apparently idiopathic abscess in the back must have its cause determined before meningitis occurs. One cannot dismiss the diagnosis because a bacterium not generally encountered in osteomyelitis has been obtained in culture. The acute nature (warmth, tenderness, redness, etc.) of the local inflammatory process should differentiate it from tuberculous spondylitis (Pott's disease). In the

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11. Patton, C. L.: Acute Osteomyelitis of Spine, Illinois M. J. **57**:268 (April) 1930.

literature, cases have been diagnosed as typhoid fever and cerebrospinal meningitis. In none of this series was this impression created. With the increase of bacteriologic knowledge, the presence of these diseases should be established rapidly. The most frequent diagnostic error has been the failure to consider the possibility of existence of vertebral osteomyelitis. A diagnosis of "toxic myelitis" should be made only after every effort has been made to rule out an epidural abscess.

SUMMARY

On the basis of sixteen cases, the subject of acute osteomyelitis of the vertebrae is presented with an analysis of the nature of the disease, its etiology, its pathogenesis, its clinical aspects, the value of roentgenograms in diagnosis, and some of the considerations underlying the prognosis and the therapeutic approach. The cases themselves are presented in detail as follows.

GROUP I. TYPE WITH ABSCESS FORMATION

CASE 1.—J. W., a man aged 31, was admitted to the hospital on May 6, 1925, with the history of a boil on the neck three weeks before admission, and pain over the left sacro-iliac region, first noticed two weeks before admission, spreading one week later to the left hip and thigh. Since the onset, the temperature had ranged between 100 and 103 F.; sweats had occurred every night, but there had been no chills.

Physical examination revealed tenderness and edema to the left of the lower lumbar vertebrae. Pain was spontaneous and increased on movement of the spine.

Course.—On May 10, there was a sense of deep fluctuation to the left of the fourth and fifth lumbar vertebrae. Aspiration yielded thick yellow pus. A diagnosis of osteomyelitis of the vertebrae was then made.

Operation.—On May 10, operation revealed an abscess cavity containing 4 drachms. (15.5 Gm.) of thick pus; in the floor of the cavity bare, rough bone was felt, which was interpreted as the left transverse process of the fifth lumbar vertebra. The cortex of this bone was removed.

Drainage was freed and convalescence uneventful.

Observations.—Bone removed at operation showed osteomyelitis.

Roentgen examination on June 9 showed rarefaction of the left upper articular process of the fifth lumbar vertebra, indicating a probable osteomyelitis.

CASE 2.—G. S., a 61 year old man, entered the hospital on Feb. 6, 1919, with a history of dull pain in the right thigh and lower part of the back for five weeks. Walking was difficult because of the pain.

Physical examination revealed a well nourished man, subacutely ill and supine, with the right hip flexed. Marked rigidity was present over the right half of the abdomen with an indefinite resistance in the right lower quadrant. On the right side of the lumbar spine were two masses, which were tender and fluctuant. The skin was reddened over them and there was marked edema of the entire lower part of the back. A Babinski sign was present on the right. The temperature was 102 F., the pulse rate 80 and the respiratory rate 20. The urine was normal.

Operation.—On February 8, an incision was made in the right costovertebral angle; several ounces of pus were obtained. The abscess cavity led down to roughened bone. On March 3, incision and drainage of the same abscess were again performed; rough bone was felt in the base of the abscess. A pocket of pus anterior to the spine was released and the wound curetted.

Course.—The temperature was normal thereafter and healing progressed uneventfully. The patient was readmitted on June 13. He was operated on twice on the second admission. On August 25, bare bone was felt with the curet. The patient was discharged on September 19, with the sinus healed. In 1921 there was a scant spontaneous discharge from the site of the scar, lasting one week; no operative indication was present.

Observations.—Urinalysis on Feb. 9, 1919, revealed no albumin or sugar; microscopic examination gave negative results.

Curettings removed at operation on March 19 showed chronic inflammatory tissue.

Roentgen examination showed: On Feb. 8, 1919, there was no evidence of a pathologic condition in the lumbar or the six lower dorsal vertebrae, except for a slight degree of spondylitis. On March 6, no evidence of pathologic condition in the lumbar vertebrae was noted. On April 2, the lumbar spine showed evidence of a slight spondylitis; however, a drainage tube present at the site of the right transverse process of the second lumbar vertebrae might have concealed a diseased area in the bone. On April 4, 1921, examination of the lumbar spine showed coalescence of the first and second lumbar vertebrae as seen in cases of old arthritis. On April 6, examination of the lumbar spine after the injection of bismuth showed the bismuth starting at the level of the fourth intervertebral space and reaching up as far as the transverse process of the second lumbar vertebra.

Case 3.—R. F., a boy aged 8 years, was admitted to the hospital on Aug. 18, 1925. He had had osteomyelitis of the right forearm and left femur four years before admission. Since then he had always been ailing. Two weeks before his admission, swelling and tenderness developed in the right lumbar region and he had an afternoon temperature of from 101 to 102 F.

Physical examination revealed, in addition to scars of previous operation on the right forearm and left thigh, a fluctuating, painful and tender mass, 2½ inches (6.3 cm.) in diameter, in the right lumbar region. The diagnosis was lumbar abscess secondary either to a renal abscess or to osteomyelitis of the spine.

Operation.—On August 19, incision and drainage of the abscess were performed. Bare bone was felt in the floor of the abscess cavity.

Course.—With adequate drainage, the wound did well and the patient was discharged on September 21, with only a slight discharge from the sinus tract. A follow-up note on Jan. 4, 1928, stated that the patient was well; no note was made concerning the lumbar region.

Laboratory Observations.—A blood count, on Aug. 19, 1925, showed white blood cells, 14,250; polymorphonuclears, 80 per cent.

A culture of pus from the abscess on August 19 revealed Staphylococcus aureus.

A roentgenogram on August 21 demonstrated evidences of a destructive process involving the bodies of the twelfth thoracic and first and second lumbar vertebrae, with crushing and fusion of these bodies.

Case 4.—I. S., a man aged 45, was admitted to the hospital on March 12, 1926, with the following history. Eighteen years before, he had had osteomyelitis of the right femur. Nine years later he was operated on, and a collection of pus was

found at the level of the first and second lumbar vertebrae behind the psoas muscle. No culture of this pus was taken. For three weeks prior to admission he had been suffering from pain in the back, progressive in nature and accompanied occasionally by fever.

Physical examination revealed evidences of mitral stenosis and insufficiency, probably rheumatic, and swelling, tenderness and spasm of the muscles to the left of the scar of the previous operation in the lumbar region. The temperature was 106 F. The diagnosis was exacerbation of an old osteomyelitis with spontaneous perforation along the scar of the previous operation.

Operation.—On March 15, an incision was made over the swollen area and pus obtained. In the base of the cavity pus was seen oozing from the bone. The necrotic bone was chipped away and the cavity drained.

Course.—The wound did well, and with a minimal discharge still present, the patient was discharged to the care of his private physician.

Laboratory Observations.—Culture of pus revealed Staphylococcus aureus.

The necrotic bone removed at operation was reported as showing evidences of acute osteomyelitis.

On March 13, 1926, roentgen examination of the lumbodorsal spine showed only evidences of hypertrophic spondylitis. In the anteroposterior position the fourth lumbar vertebra did not appear to be normal. However, in the lateral position, nothing was seen to support this view.

CASE 5.—L. G., a 51 year old man, was admitted to the hospital on Feb. 11, 1932. For seven months prior to admission he had had a discharging right otitis media. Four months prior to admission, the right preauricular region of the face was swollen for two weeks. Shortly after this the patient began to suffer from pain in the left flank and left costovertebral angle. There was fever with chilly sensations for eleven weeks prior to admission. A blood culture at another hospital three months before had revealed the pneumococcus type III.

Physical examination revealed a chronically ill looking man who could not move about because of pain in the lumbar region of the back. Both ear-drums were intact. A few shotty lymph nodes were palpable in the right anterior cervical region. The right costovertebral angle was tender, bulging and fluctuant. The left costovertebral angle was full and tender. There was shock tenderness over the lumbar spine. The diagnosis of osteomyelitis of the lumbar vertebrae was made.

Operation.—On February 13, the right and left lumbar spaces were incised. On the right side an abscess cavity containing 8 ounces (226 Gm.) of pus and a sequestrum of the right transverse process of an upper lumbar vertebra were found. On the left side an abscess cavity was encountered at the bottom of which a denuded transverse process of an upper lumbar vertebra was found. There was a communication between the abscesses across the anterior aspect of the spine.

Course.—The patient is still in the hospital with the operative wounds draining. His condition is satisfactory. Exploration of the right transverse sinus on March 13 showed complete obliteration of the sinus owing to a healed thrombophlebitis.

Observations.—A blood count on Feb. 12, 1932, showed: hemoglobin, 47 per cent; red blood cells, 2,890,000; white blood cells, 21,000; polymorphonuclears, 76 per cent.

Urinalysis showed: specific gravity, 1.012, acid, a few single white blood cells and no albumin.

A blood culture on Febrary 12, was sterile. A smear of pus obtained at operation, on February 13, showed gram-positive cocci; no tubercle bacilli were seen.

A culture yielded the pneumococcus type III. A culture of the urine on February 13 showed the pneumococcus type III and Staphylococcus albus.

Roentgen examinations were as follows: On February 12, examination of the spine showed no evidence of osteomyelitis. There was moderate hypertrophic spondylitis of the lower dorsal and lumbar bodies. On March 2, reexamination of the lumbosacral spine showed almost complete disappearance of the right transverse process of the second lumbar vertebra, and an exaggeration of the spondylitis, involving the second and third vertebrae. There was marked clouding of the entire right mastoid process.

Comment.—This is considered to be a case of otogenic sepsis, due to the pneumococcus type III, consequent on a latent spontaneously healing thrombophlebitis of the right transverse sinus, with metastatic infection of the lumbar vertebrae.

Case 6.—R. V., an infant 2 months of age, was admitted to the hospital on Sept. 10, 1923, with the history of a bluish swelling on the back of the neck, present at birth; this became hard and two weeks later discharged pus, which continued to drain up to the time of admission. For six days before admission, fever had been noticed. For five days the infant had not been able to move her left arm.

Physical examination revealed a reddened area of induration on the posterior aspect of the neck. The infant could not move either arm. The upper extremities showed flaccid hypotonia with anesthesia. The right lower extremity was spastic. Aspiration of the swelling yielded a few drops of pus.

Operation.—On September 12, operation revealed a large collection of pus under tension, deep to the erector spini muscles; in the base of the abscess rough bone was exposed, which was thought to be the left transverse process of the fifth or sixth cervical vertebra.

Course.—The wound healed satisfactorily, the motor and sensory disturbances cleared up and the patient was discharged. Convalescence was uneventful except for a period of aggravation of the symptoms of infection with transient bacteremia about September 22.

Laboratory Observations.—A blood count on Sept. 11, 1923, showed: white blood cells, 40,200; polymorphonuclears, 54 per cent.

A blood culture on September 14 was sterile. On September 22, a culture revealed 200 colonies of Staphylococcus aureus per cubic centimeter.

Cultures of the cerebrospinal fluid showed: on September 12, 24 cells and sterile fluid; on September 22, Staphylococcus albus and Streptococcus anhemolyticus; on September 23, 2 cells; on September 28, sterile fluid; on September 29, sterile fluid.

A smear of the pus from the abscess of neck removed at operation on Sept. 12, 1923, was negative; a culture was sterile.

Comment.—The nature of the swelling present on the back of the neck was not definitely ascertainable. There was no evidence to indicate that a meningocele existed. The primary condition was probably a hematoma, possibly resulting from birth trauma, which became secondarily infected.

Case 7.—R. A., a woman aged 58, was admitted to the hospital on Dec. 12, 1927, with the history of a sudden onset of pain in the right knee radiating up to

the groin, three months before admission. This persisted, was constant and lancinating and was aggravated by motion and damp weather. At the same time, the patient noted a swelling in the right groin, which was very tender and increased in size. The temperature varied from 100 to 104 F. throughout the three months. There was a loss of 30 pounds (13.6 Kg.), in three months. Roentgenograms of the spine taken outside the hospital were said to have been negative. (There was a vague history of osteomyelitis of the right twelfth rib twenty years before.)

Physical examination revealed a cachectic woman with swollen, tender right inguinal lymph nodes; the abdomen relaxed; there was no tenderness and no masses were palpable. The right knee was flexed and there was pain on extension referred to the groin. There was a small well healed scar over the right twelfth rib. The diagnosis made was that of hidden malignant neoplasm with metastases to the right groin.

Course.—On December 17, spasm of the right psoas muscle was noted, so that abscess of that muscle was suspected. The temperature rose; the patient did poorly and died on December 20.

Laboratory Observations.—A blood count showed: white blood cells 8,300; polymorphonuclears, 80 per cent.

The urine contained no albumin, sugar, casts or red or white blood cells.

A roentgenogram of the spine, taken on Dec. 19, 1927, was reported as showing a marked degree of hypertrophic spondylitis between the bodies of the twelfth dorsal, first lumbar and transverse processes of the second, third and fourth lumbar vertebrae on the left side. The left twelfth rib was markedly thickened and irregular, with areas of possible destruction. The eleventh rib also showed similar changes. The appearance of the bones suggested an inflammatory rather than a malignant process.

Autopsy.—Postmortem examination revealed a large retroperitoneal abscess along the course of the right psoas muscle containing 1 liter of greenish pus, compressing and destroying the psoas muscle. The posterior wall of the abscess was formed by dense scar tissue extending upward to the eleventh rib. The bodies of the third and fourth lumbar vertebrae were found to be eroded. The body of the third lumbar vertebra contained a rather old abscess lined by a membrane of granulation tissue near the posterior surface. There were several small abscesses in the fourth lumbar vertebra.

Pus from the psoas abscess contained hemolytic streptococci and B. pyocyaneus on culture; smear showed only gram-positive cocci in chains.

Comment.—This, then, was a case of purulent osteomyelitis of the lumbar vertebrae with the formation of a tremendous retroperitoneal abscess. The primary focus may have been an osteomyelitis of the twelfth rib on the right side, twenty years before. However, the existence of this lesion was not definitely remembered. At autopsy the ribs were not examined.

CASE 8.—L. A., a woman aged 44, was admitted to the hospital on Nov. 21, 1928. She had a history of diabetes for ten years. Two years prior to admission, she suffered from a carbuncle of the neck subsequent to which there was a series of abscesses in the right foot and leg, left leg, right clavicular region and left thigh. She entered because of pain in the right hip, knee and leg, with anorexia and vomiting for three weeks.

Physical examination revealed an undernourished, undersized woman with tenderness over the right costovertebral angle and over the spinous process of the twelfth thoracic and first and second lumbar vertebrae. The diagnoses made were abscess of the right psoas muscle and osteomyelitis of the left tibia with subperiosteal abscess.

Operation.—Five ounces (141 Gm.) of pus was evacuated from the abscess of the right psoas muscle; bare bone was not felt. Incision and drainage of the subperiosteal abscess of the left leg were also performed.

Course.—Both wounds discharged large amounts of thick pus. Postoperatively, the patient did poorly. The diabetes was not controlled well, and at one time the patient sank into stupor with ketosis, from which she was resuscitated. On Jan. 27, 1929, pain over the lower cervical spine was noticed. There was edema of the face and hands. A week later the patient began to complain of pain in the neck. There was swelling with some induration over the lower cervical region with a sense of deep fluctuation. There was marked local tenderness with pain on motion. On January 16, incision and drainage of a posterior cervical abscess, apparently extending to the spinous process of the seventh cervical vertebra, were performed. The patient did poorly and died on February 6.

Laboratory Observations.—A culture of pus from the abscess of the psoas muscle on Nov. 27, 1928, revealed Staphylococcus albus. A culture of pus from the subperiosteal abscess of the left leg on November 27 revealed Staphylococcus albus. A culture of pus from the cervical abscess on Jan. 27, 1929 revealed Staphylococcus aureus.

A roentgenogram taken on Nov. 24, 1928, showed bony abscesses in the left tibia. On Jan. 14, 1929, a roentgenogram of the cervical spine showed no abnormality in the bones, although there was an absence of the normal cervical lordosis. Whether this was due to the posture of the patient or to an inflammatory process could not be stated.

Autopsy.—Postmortem examination revealed an abscess cavity, 1 cm. in diameter, in the right transverse process of the third lumbar vertebra. From this region pus extended beneath the muscles along the inner surface of the ilium. It was this area behind the psoas muscle which had been drained by the operation. There was also osteomyelitis of the fifth cervical vertebra and of the left tibia. In addition, there were multiple metastatic abscesses of the right kidney, heart and lungs, with pyopneumothorax.

Comment.—This case was that of a patient with long-standing diabetes on whom a carbuncle developed, with resultant bacteremia and metastatic abscesses situated in the viscera and bones.

CASE 9.—D. R., a woman aged 59, was admitted to the hospital on Oct. 7, 1928, with a history of infection of the respiratory tract four weeks before admission, lasting ten days, ending by crisis and diagnosed by her physician as "pneumonia." Three weeks before admission she began to experience a dull ache in the right buttock, accompanied by tenderness on pressure, local heat and swelling. These symptoms progressed in severity up to the time of admission.

Physical examination revealed a circumscribed swelling of the right buttock with questionable fluctuation. No redness over the swelling and no glycosuria were observed. A diagnosis of abscess of the buttock was made.

An operation was performed on October 7. A large abscess cavity containing thick, greenish pus was found extending mesially to the periosteum over the sacrum, which was apparently intact.

Course.—The abscess was draining satisfactorily and the patient was doing well when, on October 24, she had a chill lasting twenty minutes and later complained of abdominal pain and tenderness. The same day, tenderness and distention became marked, and signs of fluid in the abdomen were present. Abdominal puncture was performed and pus obtained. The patient died the next day, October 25.

Laboratory Observations.—A blood count on October 24 showed: white blood cells, 13,600; polymorphonuclears, 83 per cent.

The urine was normal.

A smear of fluid obtained by abdominal puncture showed gram-positive diplococci surrounded by capsules. In a culture of abdominal pus (obtained on October 24) the pneumococcus type IV was grown.

Autopsy.—Postmortem examination revealed small necrotic abscesses in the bony substance of the third and fourth lumbar vertebrae. These communicated by a fistulous tract with the incision in the right buttock. There were also fresh adhesions over the right lower lobe of the lung. There was a generalized purulent peritonitis, consequent on perforation of a secondarily infected echinococcus cyst of the liver. A culture of pus from the vertebral abscess revealed the pneumococcus type IV.

Comment.—This is a case of respiratory infection, probably pneumonia of the right lower lobe (fresh adhesions were found there post mortem), with bacteremia, metastatic infection of the third and fourth lumbar vertebrae and a preexisting echinococcus cyst of the liver. The latter ruptured and produced a fatal peritonitis. Of interest are the following considerations:

1. The condition presented itself as an abscess of the right buttock. The etiology, namely, osteomyelitis of the vertebrae, was not established at operation nor was it suspected clinically.

2. No mention was made of tenderness over the spine in the physical examination.

CASE 10.—I. F., a youth, aged 19, was admitted to the hospital on March 11, 1928, with a history of severe pain in the right ear a month before admission. The day after the onset of the pain, myringotomy was performed and a thin purulent discharge escaped from the middle ear. The patient was doing well until three days before admission, when the discharge ceased. Two days later he again had severe pain in the right ear with a thick discharge, thicker and more profuse than previously. One week before admission he had had a chill lasting five minutes.

Physical examination revealed an acutely ill young man, with a temperature of 103.4 F., a thick, purulent discharge from the right middle ear, sagging of the canal wall and impairment of hearing. The diagnosis of acute mastoiditis was made.

Operation.—The patient was operated on on March 11. The mastoid process contained a few scattered small abscesses with little breaking down of the bone.

Course.—On March 12, there was a chill. The patient complained of headache and a bilateral Kernig sign was present. On March 13, the patient began to complain of pain in the right upper quadrant of the abdomen. This was considered pleuritic. On March 16, a pleural friction rub was heard over the right side of the chest anteriorly with diminished breath sounds. Thereafter dulness developed over

the right side of the chest posteriorly. On March 30 an abscess in the right buttock, which had gradually been forming, was incised and drained. On April 19, there was tenderness of the spinous processes of the seventh and eighth dorsal vertebrae. On April 10, pus was aspirated from the right side of the chest posteriorly.

Operation.—On April 10, thoracotomy was performed with resection of the seventh and eighth ribs on the right side. A well encapsulated cavity was found the lateral wall of which was interpreted as the external surface of the parietal mediastinal pleura. The mesal limit was the under surface of the ribs noted, and the anterolateral aspects of the bodies of the seventh and eighth dorsal vertebrae were laid bare. There was a recess leading to the body of the seventh vertebra, but at that point bare bone could not be felt. In contrast to the other, this vertebral body was tender to pressure. The abscess cavity was drained, and the patient recovered completely after an uneventful convalescence.

Laboratory Observations.—On March 11, 1928, pus from the middle ear yielded the pneumococcus type I on culture. A blood culture on March 12 revealed the same organism. Three subsequent blood cultures were sterile. A culture of pus from the abscess in the buttock on March 30 was reported as showing gram-positive diplococci overgrown by Staphylococcus albus. Pus from the mediastinal abscess on April 10 revealed the pneumococcus type I.

On March 19, a roentgenogram of the chest showed a shadow extending anteriorly from the mediastinum, considered to be a partial consolidation of the mesial half of the right lung. On April 3, a roentgenogram of the chest showed this shadow to be more extensive, denser and more sharply demarcated.

Comment.—This is interpreted as a case of acute mastoiditis with transient bacteremia after mastoidectomy, consequent metastatic abscess of the seventh thoracic vertebra, perforation and a resultant mediastinal abscess.

GROUP II. TYPE WITH SYMPTOMS OF DISEASE OF THE NERVOUS SYSTEM

CASE 11.—A. D., a woman, aged 47, had a cholecystectomy performed in October, 1926. At that time the operating surgeon reported the presence of only a single large gallstone. The patient was well until March, 1927, when she began to suffer from severe pain in the right upper quadrant of the abdomen, chills, fever and jaundice. In May, she was operated on at another hospital for the relief of these symptoms. However, a few weeks before her admission on Feb. 29, 1928, she began to suffer from abdominal pain, chills and fever.

Physical examination revealed an acutely and chronically ill woman, with jaundice, a temperature of 103.8 F., two operative scars in the right upper quadrant of the abdomen and some tenderness in the epigastrium. The diagnosis was obstruction of the common bile duct with cholangeitis.

Operation.—On March 3, the patient was operated on; a large mass of exudate was found around the common duct and porta hepatis. The common duct was dissected free and a tube placed in it, resulting in the immediate escape of bile.

Course.—Postoperatively, although there was adequate drainage of bile, the patient continued to have a high septic temperature, fluctuating between 99 and 105 F. On March 22 she began to complain of pains and paresthesias in both legs.

Knee jerks and ankle jerks were absent. There were tenderness of muscles and along the nerve trunks and impaired sensory perception, involving chiefly pain, temperature and deep muscle sensibility in both lower extremities. The diagnosis was toxic neuritis due to the long-standing infection. On March 24, the patient began to suffer from inability to void properly. On March 28, it was noted that she had a subfebrile temperature with occasional attacks of high fever. There was marked paresis of both lower extremities with beginning foot-drop, loss of both knee jerks and ankle jerks, loss of all forms of sensation in the left leg from the midcalf down and in the right leg from the knee down, and tenderness over the second and third sacral vertebrae. On March 31, the diagnosis made was epidural abscess with secondary involvement of the spinal cord at the level of the tenth dorsal vertebra. On April 1, the temperature began to mount again, the patient complained of headache, there was some rigidity of the neck and the general condition was poorer. The Queckenstedt test was performed, with the needle in the third lumbar interspace. The impression was that no block existed. Cerebrospinal fluid removed showed evidence of meningitis, but there were no clinical indications of cerebral infection. A Queckenstedt test performed on April 3 indicated the probable presence of spinal cord block. On April 4, the mentality was still clear. The next day the patient became irrational, irresponsive and later stuporous; the pulse became rapid and feeble, and death occurred on April 5.

Laboratory Observations.—A blood count on March 12, 1928, showed: white blood cells, 5,000; polymorphonuclears, 48 per cent.

Urinalysis on March 1 revealed bile, urobilin, albumin and white blood cells.

On March 1 a blood culture showed Streptococcus viridans; on March 5, no growth, on March 12, Streptococcus viridans.

On April 1, the cerebrospinal fluid was turbid and contained 10,000 cells per cubic centimeter, with 98 per cent polymorphonuclear leukocytes. Only grampositive cocci were seen on smear. These failed to grow in cultures.

Autopsy.—Postmortem examination revealed a purulent cholangeitis with multiple abscesses of the liver, one of which had invaded the main right hepatic vein, causing thrombophlebitis at that point. One centimeter from the porta hepatis there was complete stricture of the common bile duct. There were widespread metastatic abscesses in the viscera. The third lumbar vertebra was the seat of a wedge-shaped area of necrosis communicating with the epidural space. There was an epidural abscess extending from the third lumbar to the ninth thoracic vertebra. The body of the second lumbar vertebra presented several softened areas in the bone communicating with the spinal canal by means of a perforation through which a probe could be passed. Exposure of the spinal canal, in so far as it was possible, revealed the presence of a subdural abscess extending from the cauda equina to the highest point of the incision permitted (the limit was not stated; it was probably up to the midthoracic vertebrae). There was also a purulent leptomeningitis. A smear of the pus from the vertebrae revealed gram-negative bacilli (probably a postmortem invader). Cultures were not taken.

Comment.—This case was one of stricture of the common bile duct with resultant cholangeitis and cholangeitic abscesses of the liver, thrombophlebitis of the hepatic vein with resultant bacteremia and multiple metastatic abscesses. Some of these had occurred in the bodies of the second and third lumbar vertebrae, whence there occurred perforation into the epidural, then into the subdural and finally into the

spinal subarachnoid space, causing fatal leptomeningitis. This case was diagnosed in vivo. Of interest are the following considerations:

1. Clinically, tenderness had been elicited over the spinous processes of the second and third sacral vertebrae; however, at postmortem examination the osteomyelitic foci were found to be in the second and third lumbar vertebrae.

2. The first indication of the presence of vertebral disease was that of pressure on the nerve roots.

3. Although examination of the brain was not permitted at necropsy, undoubtedly a cerebral leptomeningitis must have been present. The spread of the infection from the spinal to the cerebral leptomeninges could be followed by parallel changes in the clinical condition of the patient, i. e., at first only signs of spinal cord disease and later the headache, irrationality, and stupor of cerebral disease.

CASE 12.—I. G., a 43 year old man, with a known history of diabetes for six months, entered the hospital because of pyuria, frequency and dysuria, beginning two months before admission. Later there developed urinary retention and dribbling. For two weeks there were numbness and weakness of both lower extremities, progressive up to the time of admission. Eight days before admission a bedsore developed over the sacrum.

Physical examination revealed a weakened, chronically ill looking middle-aged man. There was a large decubitus ulcer over the sacrum and buttocks. Below the level of the seventh dorsal vertebrae there was a loss of all sensation, muscular power and deep reflexes. The patient was considered to be suffering from a transverse myelitis, toxic in nature, due to cystitis.

Course.—The patient did poorly, and died the day after admission.

Laboratory Observations.—The urine contained a large amount of pus.

Autopsy.—There was a purulent cystitis with a prostatic abscess. In addition, there was an epidural abscess extending from the ninth dorsal to the sixth cervical vertebrae with extension into the right thoracic cavity and consequent fibrino-purulent pleurisy. In the muscle there was a walnut-sized abscess just opposite the intervertebral foramen between the spinous and right transverse processes of the ninth dorsal vertebra which had perforated into the epidural space. No evidence of osteomyelitis was found.

Comment.—This is interpreted as a case of purulent prostatitis with a metastatic abscess, situated in the muscle immediately opposite an intervertebral foramen, which perforated into the epidural space. Of interest are the following considerations:

1. The complication, epidural abscess, may so dominate the clinical picture that the primary etiologic condition may be clinically silent. On examination of the patient, it may be impossible to differentiate a case such as this one from one of epidural abscess secondary to osteomyelitis of the vertebra.

2. Osteomyelitis of the vertebra is not the only cause of epidural abscess.

GROUP III. TYPE WITH PAIN IN THE BACK AND FEVER

CASE 13.—C. G., a woman, aged 56, was admitted to the hospital on Sept. 11, 1930, with a history of an infection of a finger of her left hand four months before. This was followed by swelling, tenderness and redness of the entire left arm, chills, a temperature up to 106 F. and general weakness. The diagnosis was erysipelas. The fever subsided after ten days, and there followed slight desquamation of the skin of the arm. For two weeks thereafter the patient was weak. Two weeks later (three months before admission), she began to have a sharp hammering pain beginning in the sacral region, extending to both hips and thighs, occurring daily, worse at night, aggravated by motion and baking, and relieved only by drugs taken on the day before admission. Eight days before admission she was seized with a severe paroxysm of pain in the neck necessitating her going to bed. That night there was delirium. Thereafter there were a high temperature, ranging from 101 to 105 F., profuse sweats and loss of appetite. The day before admission the patient began to suffer from dyspnea and cough, with only slight expectoration.

Physical examination revealed an acutely ill woman, aged 56, who breathed rapidly, with a slight expiratory grunt, coughed occasionally, without the production of sputum, and had flushed cheeks. The temperature was 102 F., the pulse rate 110 and the respiratory rate 26. There was some dulness, with numerous coarse clicking râles over the base of the right lung where the breath sounds were somewhat diminished. There were no signs of fluid or tenderness of the ribs. There was tenderness in the right costovertebral angle. There was some tenderness on percussion over the lumbosacral and sacro-iliac articulations. The diagnosis made was that of bronchopneumonia of the right lower lobe and chronic sacro-iliac arthritis.

Course.—The clinical signs over the right lower lobe persisted unchanged. Because of tenderness over the right costovertebral angle, the diagnosis of metastatic abscess of the right kidney was temporarily entertained. About a week after admission, the patient began to have tenderness in the region of the liver. It was thought that she might have osteomyelitis of the rib and, therefore, two aspirations were made (September 18) at the level of the right fourth rib without encountering pus. A day later the patient began to complain of pain in the legs. There was cutaneous hyperalgesia present but no definite evidence of a spinal cord lesion. There was no appreciable tenderness over any portion of the vertebral column. There was a persistent plateau temperature, averaging about 104 F. On September 19, a diffuse, tender, erythematous pitting induration was seen on the posterior aspect of the right leg. This process spread progressively up to the thigh. On September 20, the patient had a slight chill, which was the first observed since admission. On September 21, exploratory aspiration of the right groin was performed; there was no pus, but some oily droplets were obtained. The patient became jaundiced, sank into stupor and died on September 22.

Laboratory Observations.—A blood count on September 11 showed: white blood cells, 18,700; polymorphonuclear leukocytes, 84 per cent.

Urinalyses on September 11 to 20 showed albumin, one plus, and a few single and very few clumped white blood cells.

Cultures of the urine on September 11, 17 and 20 yielded B. coli. A blood culture on September 11 was sterile; on September 16 a culture yielded 33 colonies of Streptococcus hemolyticus per cubic centimeter; on September 21, 225 colonies of Streptococcus hemolyticus per cubic centimeter.

On September 12, a roentgenogram of the chest showed thickening of the pleura over the right lower lobe with possible calcification. On September 16, a roent-

genogram of the abdomen, taken because of the postulated diagnosis of right perinephritic abscess, revealed only dilated bowel containing much gas.

Autopsy.—Postmortem examination revealed a suppurative spondylitis and perispondylitis involving the bodies of the fifth lumbar and first sacral vertebrae, with softening and purulent destruction of the intervening intervertebral disk. This process had spread anteriorly, causing a suppurative inflammation of prevertebral fatty tissue with suppurative thrombophlebitis of the right common iliac and external iliac veins.

Comment.—This is interpreted as a case of osteomyelitis of the vertebrae consequent on a bacteremia, probably present at the time of the infection of the left arm four months before admission. The suppurating focus perforated anteriorly and produced a purulent thrombophlebitis of the right common iliac vein with consequent overwhelming bacteremia and a fatal outcome. In the light of the postmortem knowledge, the process in the right calf, noted clinically, was considered to be due to retrograde phlebitis of the veins of the right lower extremity, although this was not definitely determined at necropsy. Of interest are the following considerations:

1. Although there was some tenderness over the sacrum and the sacro-iliac joints on admission, this did not increase and was not more marked than that elicited over the rest of the spine.

2. A flat x-ray plate of the abdomen was taken on September 16, because one of the diagnoses under consideration was a right perinephritic abscess. While it is true that this roentgenogram was not taken for the specific purpose of detecting the presence of osteomyelitis in the lumbosacral spine, nevertheless, at the time the roentgenogram was taken, the patient undoubtedly had had the inflammatory process in the vertebrae for about four months; yet on retrospect consideration of the x-ray plate, no evidence of disease in the fifth lumbar or first sacral vertebra (no lateral view) could be seen.

3. There was no clinical index of local inflammatory disease except the complaint of pain.

GROUP IV. TYPE WITH WIDESPREAD SUPPURATION

CASE 14.—D. A., a man, aged 60, was admitted on Oct. 5, 1926, with a history of severe pain in the left side of the abdomen and back, chills, fever and profuse sweats for three days.

Physical examination revealed a well developed man of 60, not looking especially ill; the tongue was coated and the pharynx reddish and dry; dulness and numerous moist râles were noted at the base of the right lung posteriorly and an inconstant sense of resistance in the right upper quadrant of the abdomen; the liver could be percussed three fingerbreadths below the right costal margin. The temperature was 98.2 F., the pulse rate 78 and the respiratory rate 20. The blood pressure was 122 systolic and 80 diastolic. The diagnosis of resolving bronchopneumonia at the base of the right lung was made.

Course.—On October 6 the patient had a chill with a rise in temperature to 104 F. Tenderness and spasticity over the right side of the abdomen and the right lumbar region were noted. A catheterized specimen of urine contained pus and a faint trace of bile. The diagnosis of right pyonephrosis was made. On October 8, a chill occurred. On October 9, cystoscopy with ureteral catheterization showed numerous white blood cells coming from both kidneys, with a few clumps of white blood cells from the right side. On October 11, herpes labialis appeared; a note was made of thick tenacious sputum. On October 13 and 20, a chill occurred. On October 21, the suspicion of a right subphrenic abscess was entertained; the right half of the diaphragm moved less than the left. The liver and subphrenic space were aspirated; no pus was encountered. On November 1, the patient had a severe shaking chill. He complained of pain in the right upper quadrant. The only physical finding elicited in the abdomen was voluntary spasm. Later that day, tenderness and a mass in the right upper quadrant developed, the conjunctivae became icteric and the liver was tender to percussion. A hepatic abscess was suspected. Bile was found in the urine the next day. On November 12 there was no disturbance in motion of the right side of the diaphragm and no tenderness over the liver on jarring. On November 20 the patient complained of pain in the lower part of the back. On November 28 he had severe pain in, and marked tenderness over, the sacrum. A low grade fever persisted. There was a varying leukocytosis.

The patient was discharged at his own request on December 2. He was readmitted on Jan. 26, 1927. He was emaciated and moribund, and kyphosis had developed over the lower part of the spine since his discharge. In the interim he had been fairly well, and had spent most of the time in bed; the only complaint was pain in the back on rising. On the day of admission, he had two severe chills, followed by profuse sweats. The temperature was 104 F., the respiratory rate 30 and the pulse rate not obtainable. The patient did poorly and died a few hours after admission.

Laboratory Observations.—Blood counts showed: on October 6, 1926, white blood cells, 41,800, and polymorphonuclears, 92 per cent; on October 7, white blood cells, 24,400, and polymorphonuclears, 94 per cent; on October 16, white blood cells 10,400, and polymorphonuclears, 76 per cent; on November 11, white blood cells, 29,000, and polymorphonuclears, 88 per cent; on November 29, white blood cells, 20,000, and polymorphonuclears, 86 per cent.

On Oct. 7, 1926, a culture of the blood yielded the Friedländer bacillus, 300 colonies per cubic centimeter in twelve hours. On the patient's readmission on Jan. 26, 1927, a culture showed: 145 colonies of the bacillus per cubic centimeter in twelve hours. On Oct. 8, 1926, a culture of the sputum yielded the Friedländer bacillus. In cultures of the urine on October 12 to 20 the Friedländer bacillus was found three times. The Wassermann reaction of the blood was negative.

From Oct. 6, 1926, to the time of the patient's discharge urinalysis repeatedly showed many white blood cells, often clumped. The reaction to the albumin test was always one plus. On November 2, bile and urobilin were present; on November 3, bile.

On Oct. 6, 1926, a roentgenogram of the chest showed deficient aeration of the base of the right lung perhaps due to a recent pneumonia. The right side of the diaphragm was slightly elevated. On October 12, the lungs showed no abnormality; the right side of the diaphragm was somewhat elevated, but not sufficiently to warrant the diagnosis of a subphrenic abscess. On November 13, the dorsolumbar spine showed a marked degree of hypertrophic spondylitis. On November 20, a roentgenogram of the chest revealed few small infiltrations of a resolving pneumonia at the base of the right lung.

Autopsy.—Postmortem examination revealed an emaciated man with a kyphosis in the region of the first lumbar vertebrae. The lungs were normal except for fibrous pleural adhesions. In the abdomen, between the hepatic flexure of the colon, liver, gallbladder and first portion of the duodenum, there was a loculated abscess containing thick green pus. In the papilla of Vater was a facetted pigment stone, 15 mm. in diameter; the common duct was not inflamed, but was greatly dilated (30 mm. wide when open) and filled with greenish-yellow pus. A few other stones were found in the bile passages. The neck of the gallbladder opened directly into an abscess in the right lobe of the liver adjacent to it, the size of a large apple. This contained greenish pus, and its wall consisted of a shaggy necrotic membrane. Parts of the necrotic walls of the gallbladder were still attached to portions of the wall of the abscess. A direct extension of the hepatic duct entered the abscess cavity. One of the smaller branches of the left division of the portal vein lying in the abscess area had become invaded and contained a purulent thrombus, which extended a considerable distance proximal and distal to its seat of primary involvement by retrograde thrombosis, but the main stem of the portal vein was free.

The kidneys were macroscopically normal; microscopically they showed cloudy swelling, infiltration of the stroma with lymphocyte and leukocyte cells and the formation of many small abscesses.

The prevertebral tissue in the region of the lumbar spine was thickened and suppurated. The first lumbar vertebra was in part destroyed, including the intervertebral disk between the first and second lumbar vertebrae.

A culture of pus from the hepatic abscess and first lumbar vertebra showed Friedländer's bacillus (Bacterium mucosum-capsulatum) in all cultures. Smears showed pus and gram-negative bacilli.

Comment.—In this case one cannot be certain whether the suppurative cholangeitis, due to Bact. mucosum-capsulatum, was primary or whether there first occurred a pneumonia caused by that organism, with bacteremia and metastatic infection of the biliary passages, obstructed by calculi in the common bile duct. The abscess of the liver was probably secondary to cholangeitis. Although no gross thrombophlebitis of the hepatic vein radicles was demonstrated, the hepatic abscess was probably the cause of the bacteremia leading to the renal and vertebral abscesses. However, all the pathologic processes found at necropsy may have been due to a bacteremia at the onset of the disease with a pneumonia due to Bact. mucosum-capsulatum. Of interest are the following considerations:

1. The unusual occurrence of a case of osteomyelitis due to Bact. mucosum-capsulatum (Friedländer's bacillus).

2. The acute development of a gibbus due to suppurative non-tuberculous spondylitis.

CASE 15.—J. R., a man, aged 30, was admitted to the hospital on Oct. 13, 1930, with the history that ten days before admission a boil developed on the back of the neck, which he squeezed during the subsequent two or three days. This was followed by complete healing of the abscess a few days later. Four days before admission, a mild pain developed in the interscapular region which rapidly became worse. On motion, the patient had sharp pain locally, with radiation down the left

side. On the next day he began to feel feverish. One day later, two days before admission, he had a shaking chill lasting an hour, which was repeated the night before admission. For the three days prior to admission, he had marked anorexia, general malaise, headache, profuse sweating and constipation.

Physical examination revealed an acutely ill man complaining of pain in the midthoracic spine. There was the scar of a well healed abscess on the back of the neck. Flexion of the neck was limited by pain in the midthoracic region, presumably due to spasm of the muscles. There was a short systolic murmur at the apex. No diastolic murmurs were heard. There was some fulness of the prostate with questionable tenderness. There was exquisite tenderness over the spinous process of the fifth thoracic vertebra with some tenderness over the spinous processes of the fourth and sixth thoracic vertebrae. To the right of the fourth thoracic vertebra there was some slight tenderness and fulness of the soft tissue. There was bilateral costovertebral tenderness. The diagnosis was Staphylococcus aureus sepsis with metastasis to the spine (fifth thoracic vertebra).

Course.—On October 14 a Kernig sign developed on the left, the knee jerks were depressed and the upper abdominal reflexes were diminished. Abdominal reflexes were not elicited on October 15. At this time, a prominence of the soft tissue was seen to the left of the spine at the level of the fourth and fifth thoracic vertebrae, construed as indicating deep suppuration.

Operation.—The patient was operated on on the night of October 15. There was no free pus found to correspond to the swelling of the soft tissue. The laminae of the fourth, fifth and seventh thoracic vertebrae were removed; the fifth thoracic seemed definitely sclerosed. An extensive epidural abscess was encountered and drained.

Course.—The patient did not do well, and died on October 19, three days postoperatively.

Laboratory Observations.—A blood count on October 13 showed: white blood cells, 18,000; polymorphonuclears, 78 per cent.

On October 14 the urine showed albumin, one plus, but was otherwise normal.

Cultures of the blood showed: on October 13, 7 colonies of Staphylococcus aureus per cubic centimeter; on October 17, Staphylococcus aureus colonies too numerous to count.

On October 14, a roentgenogram of the spine showed evidences of an old lesion at the level of the fourth and fifth thoracic vertebrae with resultant scoliosis, the convexity being to the left. There was no definite evidence of osteomyelitis.

Autopsy.—Postmortem examination revealed gram-positive cocci in a staphylococcus formation in fresh vegetations on the aortic and mitral valves. There were miliary abscesses in the lungs, liver, kidneys, spleen, colon and skin, and a recent purulent prostatitis. The body of the fourth thoracic vertebra showed suppuration in its right lateral portion. There was suppuration in the surrounding paravertebral structures and in and about the fourth right costovertebral articulation. No perforation was seen leading from the body of the fourth thoracic vertebra into the epidural space. An extensive epidural abscess was found, apparently secondary to the suppuration in and about the fourth right costovertebral articulation. On October 15, from the epidural abscess yielded Staphylococcus aureus on culture. On October 17, vegetations from the aortic and mitral valves showed gram-positive cocci in staphylococcus formation.

Comment.—This patient had an acute bacterial endocarditis, most probably secondary to squeezing a furuncle of the neck, with multiple

metastatic abscesses, one of which was situated in the fourth thoracic vertebra and gave rise to an epidural abscess. Of interest is the following consideration:

It is possible that the localization of bacteria occurred in the body of the fourth thoracic vertebra because of the existence of an old lesion of this bone, as evidenced by the x-ray plate and the sclerosed bone removed at operation, which had given rise to the scoliosis and possibly created a "locus minoris resistentiae."

CASE 16.—A. S., a man, aged 30, was admitted to the hospital on May 30, 1927, with a known history of Hodgkin's disease for two years, for which he had received roentgenotherapy with considerable relief. For two months he had been having increasing weakness and loss of weight with occasional fever. He had difficulty in breathing, and an intranasal operation was performed with some relief. There was also difficulty on urination.

Physical examination showed a markedly emaciated man *in extremis.* No lymph nodes were palpable. Murmurs were heard over the mitral and aortic areas. There was edema of the lower extremities, with evidence of fluid in the peritoneal and pleural cavities.

Course.—The patient died the day after admission, presumably with respiratory paralysis.

Autopsy.—Postmortem examination revealed a man with marked brownish pigmentation of the abdominal skin, edema of both legs, bilateral purulent bronchitis and bilateral pleural empyema. There were widespread Hodgkin's infiltrations in the lungs, liver, spleen, bone and retroperitoneal lymph nodes. There was 2,400 cc. of purulent fluid in the abdomen, secondary, probably, to multiple abscesses in the spleen. The lumbar vertebrae presented red marrow diffusely mottled by a yellowish translucent gray amorphous material. The fourth lumbar vertebra on section showed a broken-down area, the size of a cherry, filled with greenish pus. No bacteriologic studies were made.

Comment.—This case is one of widespread granulomatous disease with resulting cachexia. The widespread superimposed infection which probably arose from the purulent bronchitis, affecting especially the areas of Hodgkin's infiltrations, masked the presence of an abscess in a lumbar vertebra. In this case the latter was clinically insignificant.

ADDENDUM

Since the submission of this paper, two additional patients with vertebral osteomyelitis have been admitted to the hospital. One, a girl aged 14 years, suffered a metastatic infection of the fourth lumbar vertebra, secondary to a Staphylococcus aureus bacteremia following the squeezing of a boil. Roentgenograms of the spine taken one month after the onset of the disease showed no abnormality; one month later there was narrowing of the intervertebral space between the third and fourth lumbar vertebrae; after another month there was a kyphosis due to destruction and collapse of the fourth lumbar vertebra with almost complete disappearance of the intervertebral space between the

third and fourth lumbar vertebrae and haziness of the intervertebral space between the fourth and fifth lumbar vertebrae.

The other patient, a man of 37, had a Bacillus proteus infection of the urinary tract with Bacillus proteus bacteremia and metastatic infection of the sixth cervical vertebra. Roentgenograms taken about three weeks after the onset of the disease showed narrowing of the intervertebral space between the fifth and sixth cervical vertebrae; five weeks later, roentgenograms showed destruction and collapse of the sixth cervical vertebra.

In each of these cases, roentgenograms afforded evidence confirmatory of the clinical diagnosis of vertebral osteomyelitis. A point worth stressing is that in each case an intervertebral space adjoining the diseased vertebra was definitely narrowed before there was certain abnormality in the appearance of the diseased bone itself.

SPONTANEOUS NONTRAUMATIC PERIRENAL AND RENAL HEMATOMAS

AN EXPERIMENTAL AND · CLINICAL STUDY

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CHICAGO

A few years ago, during work on a series of experiments on the renal veins, it was observed that marked hemorrhage was frequently associated with venous obstruction of the kidney. In several instances a large perirenal hematoma followed complete ligation of the renal vein. Subcapsular and parenchymal hemorrhages were present constantly in the large, tense, congested kidneys.

It occurred to us that certain cases of spontaneous nontraumatic perirenal hematomas in man might find an explanation in venous congestion of the kidneys, with the resultant elevated vascular pressures and possible capsular ruptures.

We divided our investigations into three kinds of research: (1) the clinical study of a personal case, (2) the experimental ligature of the renal veins in animals and (3) the etiologic study of cases collected from the world's literature.

We believe that elevation of intracapsular and vascular pressure in the kidney can, and probably frequently does, produce spontaneous hemorrhages and even ruptures of the renal capsules with resultant perirenal hematoma. This action would be favored by renal diseases and slight traumas.

By the term "perirenal hematoma" we include subcapsular and extracapsular hematomas and renal and pararenal hemorrhagic cysts. Hemorrhagic renal cysts have been included by so many earlier writers in discussions of perirenal hemorrhage that any complete study of the literature must again include them, unless one attempts a reclassification.

At the German Surgical Congress in 1912, Professor Ritter advised ligature of the renal veins in tuberculosis of the kidneys when nephrectomy was not advisable. He explained that, in animals, ligature of the renal vein produced a long-continued congestion of the kidney. In

the course of from three to five weeks there resulted an atrophy of the kidney by fibrosis, the kidney being reduced to about one third of its normal size. He noticed the production of hemorrhages similar to the forms of perirenal hematomas found in man.

We hope to give some evidence that spontaneous hematoma in man is quite similar in cause and effect to hematoma produced in animals by ligature of the renal vein.

The following is a report of a case of perirenal hemorrhage seen by us, in which the patient recovered following operation, though the causative factor was never demonstrated.

REPORT OF CASE

Complaint.—Mrs. L. P., a white woman, aged 39, began her regular menses on April 30, 1931, and as usual was quite comfortable. At 3:30 a. m. on May 5, she was awakened by a terrific pain in the lower right abdominal quadrant which "felt as though something inside were twisting." She was nauseated and vomited four times following her abrupt awakening at 6 a. m. At 6:30 a. m., she was given a hypodermic of morphine. At that time a large mass was felt in the right side of the abdomen and was thought to be a large ovarian cyst with a twisted pedicle. Menses continued as usual. She was sent to St. Luke's Hospital that morning.

History.—The past history was irrelevant except for a round ligament shortening six years previously.

The family history was unimportant.

Inventory of the various systems likewise gave negative results. There had been no loss of weight, dysuria or hematuria. There was no history of trauma, though the patient had been doing some house cleaning the day before, and had done considerable stretching with her right arm in reaching the ceiling.

Examination.—At the hospital, examination revealed a well nourished, rather obese, white woman, lying quietly in bed, not acutely ill. Slight pallor was present. The head and neck were normal; the lungs were clear; the heart was rapid; the blood pressure was 138 systolic and 92 diastolic. The abdomen was obese and relaxed, and there was a mass the size of a grapefruit just above the level of the umbilicus on the right. Its lower border extended into the pelvis. It was movable, doughy to pressure and moderately tender. The reflexes were normal. A vaginal examination revealed no definite connection with the uterus. The temperature was subnormal; the pulse rate, 90, and the respiratory rate, 20.

Laboratory examination showed: red blood count, 3,840,000; white blood count, 18,300; hemoglobin, 75 per cent. The urine (voided specimen) was amber and acid, with a specific gravity of 1.035; it contained more than 50 mg. of albumin per hundred cubic centimeters, many erythrocytes and from 15 to 20 pus cells per high power field. The Wassermann reaction was negative. Catheterized urine showed no blood.

Roentgen examination by Dr. E. L. Jenkinson revealed a mass in the right side of the abdomen pressing against the cecum and displacing is medially. It obscured the shadow of the right kidney and the lower border of the liver.

Course.—On May 7, the pain became more severe, but the mass was smaller. The red blood count had dropped to 2,760,000; the hemoglobin was

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Course.—On May 7, the pain became more severe, but the mass was smaller. The red blood count had dropped to 2,760,000; the hemoglobin was

50 Gm.; the opposite kidneys weighed 40 and 38 Gm., respectively. Rupture of the renal capsule was seen in dog 15.

Dogs 11 and 12.—These animals were killed on the seventh day, and dog 8 died on the same day (of sepsis); all showed perirenal hematomas. The hematoma was large (weight not taken) and infected in dog 8, and rupture of the capsule could be seen. The hematoma was small in dog 11, although the renal mass weighed 206 Gm., against 42 Gm. on the opposite side. The excessive size and weight were due to parenchymal and subcapsular bleeding. The hematoma and subcapsular bleeding were slight in dog 20, the kidney operated on weighing 68 Gm.; the healthy kidney weighed 34 Gm.

Dogs 3 and 10.—These dogs were killed on the eighth day. Both showed renal and some subcapsular hemorrhage, but no perirenal hemorrhage. In dog 10 the kidneys weighed 28 and 26 Gm., respectively, and appeared somewhat congested, with small hemorrhages in the parenchyma. The collateral circulation was not larger than usual.

Dog 2.—This dog was killed on the eleventh day. There was considerable subcapsular and parenchymal hemorrhage, but no extracapsular hemorrhage. (The weights were not taken.)

Dogs 5 and 6.—These animals were killed on the thirteenth day. Dog 5 had subcapsular hemorrhages, but no extracapsular hemorrhage; the kidney operated on weighed 24 Gm. and was firm and sclerotic. Dog 6 showed only small renal hemorrhages, but no subcapsular or extracapsular hemorrhage. The kidney operated on was small, firm and sclerotic and weighed 12 Gm. It evidently was undergoing atrophy by fibrous changes.

Dog 9.—This dog was killed on the fifteenth day. Pyelonephritis and suppurating perirenal hematoma were found on the side on which operation was performed. The kidney operated on weighed 62 Gm., as against the one not operated on, 28 Gm.

Dog 4.—This animal was killed on the twentieth day. Subcapsular and parenchymal hemorrhages were found. The kidney operated on was half normal size, weighing 15 Gm., and was atrophic and sclerotic to gross examination. Dog 21 died of distemper on the twentieth day, but autopsy was not obtained.

Dog 22.—This animal was killed on the twenty-fifth day. A small encapsulated perirenal hematoma lay below the inferior pole of the kidney operated on. The kidney was sclerotic and atrophic and weighed 12 Gm. The opposite kidney was normal in appearance and weighed 24 Gm.

Dogs 17, 18, 19 and 20.—These dogs were killed on the thirty-third day. In dog 17, the kidneys operated on had a curious appearance. It was calcified throughout and had incrustations in the renal pelvis. No intrarenal, subcapsular or perirenal hemorrhages were present. The kidney weighed 16 Gm. The opposite kidney was healthy and weighed 52 Gm. Dog 18 had a perirenal hematoma below the lower pole of the kidney operated on, which was small (18 Gm.). The kidney not operated on weighed 32 Gm. and was quite healthy.

Dogs 19 and 20 showed subcapsular and parenchymal bleeding, but no massive hematomas. The kidney operated on in dog 19 weighed 34 Gm. and the opposite one, 30 Gm. The kidney operated on in dog 20 weighed 8 Gm. and was markedly atrophic and sclerotic. The other kidney, which was not operated on, weighed 36 Gm. and appeared normal.

Of the 5 operative deaths, 1 dog died of distemper, an intercurrent malady entirely outside of our investigations. So we must figure that 4 of our 21 dogs died (19 per cent). One bled to death (4.76 per cent). Three were infected (14.2 per cent).

Atrophy and a reduction in size of the kidneys operated on occurred in 6 cases (28.57 per cent), the atrophy becoming apparent after the second week. The kidney not operated on showed no change.

The histology of the calcified kidney showed an almost complete sclerosis of the cortex, although many tubules and glomeruli still persisted. Numerous small calculi were distributed throughout the renal

TABLE 1.—*Ligation of Renal Veins in Dogs* *

Dog	Duration of Life, Days	Hematoma	Weight of Kidney Operated On, Gm.	Weight of Opposite Kidney, Gm.	Results
1	1	None	..	..	Died of peritonitis
2	11	Subcapsular	..	..	Killed
3	8	Subcapsular	..	..	Died of hemorrhage
4	20	Subcapsular	15	..	Killed
5	13	Subcapsular	24	..	Killed
6	13	None	12	26	Killed
7	3	None	..	..	Died of peritonitis
8	7	Perirenal	..	..	Died of sepsis
9	15	Perirenal	62	28	Killed; infected hematoma
10	8	None	28	26	Killed; hematoma
11	7	Perirenal	206	42	Killed; hematoma
12	7	Perirenal	68	34	Killed; hematoma
13	3	Perirenal	198	38	Killed; hematoma
14	3	Perirenal	82	26	Killed; hematoma
15	5	Perirenal	117	40	Killed; hematoma
16	5	Subcapsular	50	38	Killed; hematoma
17	33	None; calcified kidney	16	52	Killed; hematoma
18	33	Perirenal	18	32	Killed; hematoma
19	33	Subcapsular	34	30	Killed; hematoma
20	33	Subcapsular	8	36	Killed; hematoma
21	20	No examination	..	..	Died of distemper
22	25	Perirenal	12	24	Killed

* Died 5 (22.7 per cent); subcapsular 7 (33.3 per cent); hematoma 76 per cent; perirenal 9 (42.8 per cent); no hematoma 5 (23.8 per cent).

parenchyma, mostly in the cortex. Some incrustations adhered to the renal pelvis also.

REVIEW OF THE LITERATURE

A review of the literature yielded 178 cases of spontaneous nontraumatic perirenal hematomas. A few additional cases mentioned by various authors were not included because the articles describing them were not available and the details were unobtainable. Such were the cases reported by Dumreicher, Güterbock, Miller, Friedler, Ponfick, Pritchard, Rosenburg, Rose, Schmorl, Turco, Traube, Wildbolz, Yoshikama and Zeno. Some of these may be true cases of perirenal hematoma. In others the details were too few, or were entirely lacking, as in the cases of Rose and Dumreicher, reported by Etcheverry. In

the traumatic forms described by Danyau, Gruber and Rouppe spontaneous bleeding developed long after the trauma, so may be considered in our list as spontaneous ruptures. Marshall's case was traumatic also, but is included as an infected hematoma. The cases reported by Hogge, Bilschai and Parrot were short of details, but we believe that they should be included. Of the hemorrhagic cysts reported by Etcheverry, the cases of Piorry, Bellamy, von Brackel and Recamier should be included. Recently Munger reported 19 cases of acute hemorrhagic cysts of the kidneys, which probably belong here as parenchymal or subcapsular hematomas. To our cases he added those of Siredey, Lancereaux, Maisonneuve, Poirier, Guiliani, Begg, the Mayo Clinic (2 cases), Wolff (2 cases), Roussel and his own. Of the suprarenal hemorrhages reported by Droubaix, the cases of Rayer, Droubaix and

TABLE 2.—*Ages*

Years	Number of Cases
0 to 10	4
11 to 20	12
21 to 30	25
31 to 40	38
41 to 50	34
51 to 60	27
61 to 70	11
71 to 80	1
81 to 00	2
Old man	1
No record	22
Total	178

Chiari may be considered. Actually, we have assembled 200 cases, only 178 of which were analyzed.

Age.—The ages in the 178 cases ranged from 6 days to 89 years. In 70 per cent of the cases the ages ranged from 20 to 60 years, and in 40 per cent, from 30 to 50 years. Thus hematoma is seen to occur most frequently during active adult life and rarely in the extremes of life.

Sex.—Males were attacked more often than females: males 91; females 64; not recorded 23. A ratio of 3:2 obtains. In some articles the ratio was 2:1.

Conditions.—Subcapsular hematomas, including blood cysts, occurred in 37 of 200 cases, or 18.5 per cent, and extrarenal hematomas in 163 cases, or 81.5 per cent. Parenchymal bleeding is recorded in nearly every case examined histologically. Renal blood cysts are mentioned in 23 cases (11 per cent), pararenal blood cysts in 6 (3 per cent) and hematonephrosis in 8 (4 per cent).

Our experimental work showed parenchymal bleeding in all cases. The extrarenal hematomas varied in size from small blood clots just below the lower pole to extensive perirenal masses completely surrounding the kidney. The subcapsular bleeding varied likewise from multiple petechiae under the capsule to large subcapsular blood masses. A complete hematonephrosis or true hematic renal cysts were not obtained in this series.

Subcapsular hematomas were recognized in 7 dogs, or 33.3 per cent, of our 21 animals, and extrarenal hematomas in 9, or 42.8 per cent. Thus perirenal hematoma occurred in 76 per cent of our experiments on animals and parenchymal bleeding in all (100 per cent).

The causes of perirenal hematomas suggested by various authors are numerous. The cause in certain instances was definite, while in others

TABLE 3.—*Renal Conditions Alone as Registered in Our 178 Cases*

Conditions	Cases
Nephritis	30
Renal tumors	22
Aneurysm of renal artery	20
Arteriosclerosis	12
Hydronephrosis	7
Periarteritis	7
Renal tuberculosis	4
Renal lithiasis	3
Cystic kidney	3
Erosion of renal artery	2
Thrombosis of renal vein	1
Renal congestion (prostatism)	1
Total cases	112 or 63% } 69%
Suprarenal conditions	11 or 6%

it was suggested by the associated pathologic changes. The causes may be divided into 7 groups, as follows:

1. Trauma is the most frequent cause. It is not considered in this article.

2. Diseases of the kidneys were causative in 112, or 63 per cent of 178 cases, and included, in the order of frequency, nephritis, tumors, hydronephrosis, infections, tuberculosis, lithiasis, cystic disease, etc. Diseases of the suprarenals occurred in 11, or 6 per cent of the analyzed cases; diseases of the kidneys and suprarenals together comprised 69 per cent of the cases.

3. Diseases of the blood vessels occurred as causative factors in 29.2 per cent, and as associated pathologic processes in 36 per cent of our 178 cases. Included here were arteriosclerosis, aneurysms, periarteritis nodosa, infarcts and thrombosis.

4. Diseases of the blood were incriminated in 4.5 per cent of our 178 cases. Included were hemophilia, polycythemia, leukemia, scurvy, purpura and Hodgkin's disease.

5. Infections were located as causative in 10 per cent and as the pathologic change present in 13.4 per cent of our cases. The infections were renal, extrarenal and general, and included the following: renal tuberculosis, sepsis, appendicitis, prostatitis, pyelonephritis, perinephritis, scarlatina, malaria, typhoid fever, syphilis and pyemia.

6. Diseases of the retroperitoneal tissues occurred in a few cases. Such were perinephritis, erosion of the arteries, embolism, thrombosis, suprarenal hemorrhages and aortic diseases.

7. No cause was given in 26 cases, or 14.6 per cent.

Renal congestion and hypertension can and do occur in nearly all these conditions, and are particularly prone to appear in nephritis, arteriosclerosis, hydronephrosis, periarteritis nodosa, lithiasis, cystic kidney, thrombosis of the renal vein and prostatism. Clinically, then, we may conclude that congestion and renal hypertension may occur more or less often and be a factor in the causation of bleeding and perhaps rupture of the kidney, especially when associated with pathologic conditions.

PATHOLOGIC ANATOMY

Whatever the cause may be, the renal hemorrhage is always parenchymal; it may remain subcapsular or become perirenal, and it varies from small ecchymoses to large hematomas.

The renal hemorrhage is usually acute and extends rapidly and progressively in all directions, mostly downward toward the iliac fossa, into the mesentery and along the large abdominal vessels. Hematuria may or may not be present. The usual course is progressively downward, with a tendency toward exsanguination.

The pressure in the hematoma may eventually equal the arterial pressure, and clotting may stop the hemorrhage, with a tendency toward recovery.

Rarely the hematoma may migrate and rupture into the peritoneal cavity or into any of the abdominal viscera.

The hemorrhage may resorb more or less completely, and cure may be established spontaneously by resolution. It may organize into a mass of firm fibrosis. It may become encapsulated by fibrous tissue or undergo central degeneration and absorption with the eventual formation of renal or pararenal cysts. It may be infected by direct extension of inflammations from the kidney or adjacent organs or by a blood-borne infection.

Large subcapsular hemorrhages will at times denude the entire kidney of its capsule to form a good-sized cyst in which the kidney lies, either as a healthy or as a more or less degenerated organ. Legueu reported cases of this kind and designated them "hemato-nephrosis."

Smaller subcapsular and parenchymal hematomas may form a type of hemorrhagic renal cyst.

Cases of hematonephrosis were reported by Kirmisson, Legueu, Fowler, Krogius, Baló and Connerth.

Hemorrhagic cysts of the kidney were reported by Amberger, Cibert, Körte, Gouget and Souligoux, Piorry, Recamier, Lancereaux, Wolff, von Brackel, Armstrong, Guiliani, Begg, Maisonneuve, Mayo, Munger, Poirier, Roussel and Siredey.

Extrarenal blood cysts were reported by Bellamy, Leopold, Malherbe, Picqué, Walther, Minkowski, Friedrich, Lippens, Fedoroff, Hullsiek and Sohn. They may or may not connect with the kidney.

Old organized sclerotic hematomas were reported by Gyselynck and by Kümmel.

Infected hematomas occurred in the cases of Marshall, Michaux, Körte and Floyd and Pittman, perinephritis being the diagnosis in the cases of Schultze, Peters, Baló and Sturm. General sepsis as well occurred in the cases of Brunner and Heilmann. Grasmann recorded a septic infarct; Joseph, a suppurative nephritis, and Pauchet, Meyer, Lediard and Meyer and Singer, cases of infected kidneys.

The infections were both general and local and were found to be causative as well as complications. They had a tendency to favor congestions of the kidneys with resultant edemas and elevated renal and vascular tensions. Infections seemed to favor renal hemorrhages and capsular ruptures. It was for this reason that the cases of infected hematomas of Marshall and others were included.

Rupture of the renal capsule was mentioned in 30 cases (16.9 per cent) as follows: Azzurrini, Amberger, Armstrong, Babitzki, Baló, Boland, Bevacqua, Baxter, Cibert, Dickinson, Fedoroff, Floyd and Pittman, Doll, Fowler, Le Clerc-Dandoy, Lenk, Läwen, Hueter, Hullsiek, Hinz, Ilyin, Janssen, LeComte, Meyer, Mertens, Prym, Rosenbach, Schiffmann, Speese, Secrétan and Thomas.

As to the frequency of renal rupture as found at autopsy, we may mention that Küster found it in 0.12 per cent of 7,741 necropsies; Herzog in 16 or 7,805 autopsies, and Güterbock in 10 per cent of 326 autopsies. Henline found 25 cases of spontaneously ruptured kidney in the literature in 1924. Lepoutre assembled 10 cases of ruptured hydronephrosis in 1928.

Hullsiek (1931) computed the number of nontraumatic ruptures of the kidney at 30.

The tendency to rupture is much greater in a diseased than in a healthy kidney. This is especially true in chronic conditions. such as nephritis, arteriosclerosis, lithiasis, hydronephrosis. tuberculosis, neo-

plasms and polycystic disease. Although it is admitted that various forms of trauma, even mild, may be the chief causes of rupture, nevertheless, sudden congestions with elevated intrarenal pressure may play an important rôle in the mechanism of this rupture.

If we accept Tuffier's classification of renal rupture, as ecchymosis, subcapsular rupture and total rupture, then congestions, especially acute types, will assume particular importance (1892).

The cardinal symptoms of the commonly seen acute forms are sudden, sharp, severe pain in the region of the kidney; an abdominal retroperitoneal tumor felt below the costal margin, which rapidly and progressively increases in size, and the signs of internal hemorrhage: such as shock, marked anemia, pallor, cold sweats, clammy skin, prostration, subnormal temperature, low red cell count and low hemoglobin.

In the early stages, or in the forms with an insidious course, only one, or indeed none, of these cardinal symptoms may be present. The later appearance of severe secondary anemia and abdominal tumor or dulness should clear up the doubtful diagnosis in such cases.

The hemoglobin may be quite low, but rarely sinks below 45. The hemoglobin ranged from 45 to 80 in most of our cases. The red cell count is rarely below 3,000,000.

In the absence of a tumor, a dulness in the flank may be elicited at times. The first symptom is almost invariably pain, and tumor soon follows as a close second.

Many cases show gastro-intestinal disturbances, such as nausea, vomiting, meteorism, constipation and ileus. These symptoms are much more marked in the presence of trauma.

The temperature is subnormal at first, but later rises, due to the absorption of fibrin or to infection.

Rigidity of the muscles about the costovertebral angle and upper part of the abdomen is often present, and is more marked when infection ensues or in renal disease.

Hematuria and evidences of nephritis in the urine are frequent findings. Our records show mention of nephritis in 30, or 16.8 per cent. Coenen found pathologic urine in more than 53 per cent. Urinary disturbances are not infrequent, being present as a sign of renal or bladder diseases. Chills, fever and pyuria occur only with associated urinary infections or secondarily infected hematomas. Calculi are occasionally discovered by the roentgenogram.

Lumbar swelling and ecchymosis on the skin rarely appear and are pathognomonic of deep lumbar and perirenal disease.

Exploratory puncture may assist, but usually it fails to clear the diagnosis, since only bloody fluid is obtained.

The tumor was unilateral in 105 cases, 46 on the right and 59 on the left. Six cases were bilateral.

The course was acute and rapidly progressive in the typical severe cases. The chronic forms with slow insidious course and of long duration were described by Cathelin, Lenk and Koch. Such, however, are not frequent. Ordinarily the hemorrhage is progressive, and the tumor grows steadily from day to day. The pain continues severe. The duration of the severe cases is necessarily quite short and varies considerably. Table 4 records the duration of some of the cases to the time of operation or death.

Death may be due to secondary anemia, the result of massive hemorrhage. Other conditions that may be fatal are ileus, pneumonia, peritonitis, sepsis, uremia or operative shock.

The condition has been diagnosed correctly in only a few cases. It is usually confused with the causes of acute conditions within the

TABLE 4.—*Duration of the Disease*

Case	Duration	Case	Duration
Rapin	12 hours	Doll	5 days
Prym	24 hours	Lenk	6 days
Schlichting	24 hours	Pauchet	9 days
Tuffier	24 hours	Michaux	10 days
Waegner	24 hours	Joseph	12 days
Seidel	24 hours	Löwen	13 days
Mackenzie	25½ hours	Hildebrand	3 weeks
Piek	2 days	Minkowski	6 weeks
Oestreich	3 days	Cathelin	3 months
Schäfer	4 days	Koch	1 year
Ledlard	4 days	Lenk	1 year

abdomen. It must be differentiated from hydronephrosis, renal lithiasis or tumor, paranephritic abscess, aneurysm of the renal artery, appendicitis, ruptured gallbladder or gastro-intestinal ulcers, torsion of an ovarian cyst, ruptured ectopic pregnancy, etc.

The cardinal symptoms of renal pain, abdominal tumor and signs of internal hemorrhage should furnish a definitive diagnosis in favorable cases.

The prognosis is dependent to some extent on the origin of the bleeding, its cause and the kind of treatment given, as well as on the general condition of the patient. It is bad in cases in which treatment is not given and in cases with severe renal pathologic changes or a ruptured aneurysm. It is favorable after early nephrectomy and in congestive forms. Severe cases tend toward death.

TREATMENT

The treatment in 47 cases was conservative and expectant and resulted in a mortality of 100 per cent. All authors reported death in

all cases in which treatment was not given: Coenen, Greco, Israel, Rapin, Speese, Seidel, Tschmarke, Abbetti, Babitzki, Bonthius, Mackenzie, Meyer and Singer, Vogeler and others.

Conservative surgical procedures, consisting of the evacuation of blood clots, tamponage and drainage, gave better results. In 43 cases in which the patients were so treated there was a mortality of 40 per cent.

Surgeons soon learned that the kidney was often at fault, and that nephrectomy gave the best results. Sixty-two patients were nephrectomized, with a mortality of 24 per cent.

Of the 174 patients, 98 died (56.35 per cent) and 76 were cured (43.65 per cent).

TABLE 5.—*Results of Treatment in 178 Cases*

	Cases	Cured	Died	Mortality, Percentage
Nephrectomy	62	47	15	24.3
Drainage	43	26	17	40.0
Laparotomy	8	2	6	75.0
Operation	6	1	5	83.0
Hysterectomy	2	0	2	100.0
Decapsulation	1	0	1	100.0
Aspiration	1	0	1	100.0
Herniotomy	1	0	1	100.0
Appendectomy	1	0	1	100.0
Exploratory	1	0	1	100.0
Cholecystectomy	1	0	1	100.0
No operation	47	0	47	100.0
Grand total	174	76	98	
No records	4			
Final total	178	43.65%	56.35%	

Greco assembled 60 cases, in 40 of which the patients were operated on, with cure in 28; 62 per cent by incision and 83 per cent by nephrectomy. The total mortality was 53.3 per cent.

Seidel reported 18 cases, with a mortality of 41.7 per cent for the 12 cases in which the patients were operated on.

Israel showed a total mortality of 60 per cent, Rapin 50 per cent, Meyer and Singer 60 per cent and Speese 47.5 per cent.

Tschmarke collected 38 cases; in 27 of these operations were performed within twenty-four hours; 13 patients were cured (48 per cent), and 14 died (52 per cent). The remaining 11 patients were operated on late, after a lapse of several weeks, and only 1 died (9 per cent). We might inquire how many of the 27 patients who were operated on early would have lived for several weeks without treatment.

Nephrectomy is the operation of choice, unless a bleeding vessel can be caught and ligated, as in cases with extrarenal etiology.

Table 6.—*Cases Collected from the Literature* *

Author	Year	Sex; Age	Location	Cause and Pathologic Condition	Treatment	Result
Ahbetti................	1912	F, 49	Subcapsular	Arteriosclerosis	Nephrectomy	Cured
Amberger..............	1926	M, 36	Extrarenal	No cause; nephritis; arteriosclerosis; cystic kidney	Nephrectomy	Cured
Armstrong...	1895	M, 50	Extrarenal	Nephritis and renal cavity as cause (cyst); aneurysm of renal artery	None	Died
Azzurrini.............	1912	F, 36	Extrarenal	Nephritis	Hysterectomy	Died
Babitzki.............	1912	F, 36	Extrarenal	Hydronephrosis	Nephrectomy	Cured
Barnard..............	1900	Little girl	Extrarenal	Aneurysm of renal artery	None	Died
Baggerd..............	1914	M, 44	Extrarenal	Hydronephrosis as cause; nephritis	Nephrectomy	Died
Barthels.............	1930	F, 51	Extrarenal	Suprarenal	Decapsulation of kidney	Died
Bazy.................	1905	M, old	Extrarenal	Nephritis	Drainage	Died
Baxter...............	1921	F, 15	Extrarenal	Nephritis as cause	Laparotomy	Cured
Bevaequa.............	1914	M, 37	Extrarenal	Nephritis as cause; arteriosclerosis; miliary aneurysms	None	Died
von Beck.............	1912	......	Subcapsular	No cause	Nephrectomy; nephrotomy	Cured
Boland...............	1923	F, 51	Extrarenal	Sarcoma of kidney	Nephrectomy	Cured
Bonthius.............	1931	F, 55	Extrarenal	No cause; suprarenal suspected	Nephrectomy	Cured
Bellamy..............	1885	F, 44	Subcapsular	No cause; renal blood cyst	Nephrectomy	Died
Bollag...............	1920	M, 21	Extrarenal	Hemophilia	Drainage	Died
Breitner.............	1923	F, 22	Extrarenal	No cause; suprarenal ruptured	Drainage	Died
Brunner..............	1927	M, 41	Extrarenal	Sepsis as cause	None	Died
Brunner..............	1927	F, 55	Extrarenal	Suprarenal hemorrhage	Drainage	Died
Baló.................	1925	M, 33	Extrarenal	Hypernephroma	Nephrectomy	Cured
Baló.................	1925	M, 13	Subcapsular	Nephritis	Nephrectomy	Cured
Baló.................	1925	M, 78	Subcapsular	Hydronephrosis as cause; arteriosclerosis	None	Died
Baló.................	1925	F, 44	Subcapsular	No cause; hematonephrosis	Nephrectomy	Cured
Baló.................	1925	F, 55	Extrarenal	Hydronephrosis and arteriosclerosis as causes; carcinoma of uterus	Laparotomy	Died
Baló.................	1925	F, 18	Extrarenal	Aneurysm of spermatic artery ruptured	Herniotomy	Died
Baló.................	1925	F, 26	Extrarenal	Aortic aneurysm	Appendectomy	Died
Baló.................	1925	M, 56	Extrarenal	Aortic aneurysm	None	Died
Baló.................	1925	M, 23	Extrarenal	Hemophilia cause; perinephritis	Aspiration	Died
Bilsehai.............	1928	......	Extrarenal	Toxic nephritis		
von Braekel.........	1899	M, 18	Subcapsular	Blood cyst of kidney	Resection	Cured
Begg.................	1926	M, 33	Subcapsular	Blood cyst of kidney	Nephrectomy	Cured
Cathelin.............	1907	F, 25	Subcapsular	Tuberculosis of kidney	Nephrectomy	Cured
Cathelin.............	1907	......	....	Tuberculosis of kidney		
Chauvin.............	1930	M, 41	Extrarenal	Epithelioma of ureter	Nephrectomy	Died
Chauvenet............	1928	F, 59	Extrarenal	None	Drainage	Died
Cibert...............	1928	......	Extrarenal	Cyst of kidney	Nephrectomy	Cured
Coenen...............	1910	M, 33	Extrarenal	Hemophilia as cause; nephritis	Nephrectomy	Died
Connerth.............	1923	M, 20	Extrarenal	Hydronephrosis; old hematonephrosis	None	Died
Cordier..............	1910	M, 60	Bilateral extrarenal	Suprarenal hemorrhage	None	Died
Chisholm.............	1926	F, 28	Extrarenal	Aneurysm of renal artery	Laparotomy	Died
Danyau...............	1835	M, 15	Extrarenal	Aneurysm of renal artery; trauma 1 month before	None	Died
Dickinson............	1883	......	Extrarenal	Nephritis	None	Died
Doll.................	1907	M, 60	Extrarenal	Arteriosclerosis cause; nephritis	No operation	Died
Doll.................	1907	M, 41	Extrarenal	Arteriosclerosis cause	No operation	Died

* Additional cases (Wunderlich, Wildbolz, Traube, Turco, Schmorl, Pritchard, Ponfick, Miller and Israel) are mentioned in the literature, but we were unable to find details.

TABLE 6.—*Cases Collected from the Literature* *—Continued*

Author	Year	Sex; Age	Location	Cause and Pathologic Condition	Treatment	Result
Donati	1924	M, 55	Extrarenal	No record	Operation	Cured
Droubaix	1887	F, 62	Extrarenal	Suprarenal	None	Died
Dorendorf	1927	M, 46	Extrarenal	Arteriosclerosis cause; aneurysm of renal artery	None	Died
Dourlin	1803	M, 55	Extrarenal	Aneurysm of renal artery	None	Died
Eenrius	1928	......	Extrarenal	Hypernephroma	Operation	Died
Eenrius	1925	......	Extrarenal	Aneurysm of abdominal aorta	Operation	Died
Eigler	1928	M, 67	Extrarenal	Aneurysm of aorta	None	Died
Eigler	1928	M, 51	Extrarenal	Hypernephroma	Laparotomy	Died
Engel	1906	F, 82	Extrarenal	Aneurysm of renal artery; also arteriosclerosis	None	Died
Fedoroff	1925	F, 35	Extrarenal	No cause; pararenal cyst	Drainage	Cured
Fedinec	1929	F, 33	Extrarenal	Suprarenal	Drainage	Died
Fishberg	1923	M, 63	Extrarenal	Periarteritis nodosa	No record	Died
Floyd and Pittman	1931	M, 39	Extrarenal	Calculus and ruptured kidney as cause; perinephritic abscess	Drainage	Cured
Frazier	1908	M, 27	Extrarenal	Tuberculosis of kidney	Drainage	Cured
Franke	1912	M, 33	Extrarenal	Hypernephroma	Nephrectomy	Cured
Friedrich	1906	M, 22	Subcapsular	Polycythemia as cause; pararenal cyst	Drainage	Cured
Fowler	1911	F, 52	Extrarenal	No cause; cavity in kidney (cyst)	Nephrectomy	Cured
Gile	1929	M, 37	Subcapsular	Hemangioma of kidney	Nephrectomy	Cured
Gaál	1930	M, 47	Extrarenal	Leukemia	Operation	Died
Greco	1925	M, 51	Extrarenal	Prostatism and congested kidneys	Drainage	Cured
Greco	1925	F, 43	Extrarenal	Aneurysm of renal artery	Drainage	Died
Grasmann	1923	F, 36	Extrarenal	Septic infarct of kidney	Nephrectomy	Cured
Gruber	1926	M, 39	Extrarenal	Periarteritis nodosa as cause; traumatic aneurysm of renal artery	None	Died
Goldmann	1912	F, 8	Extrarenal	Sarcoma of kidney	Nephrectomy	Cured
Gouget and Souligoux	1905	F, 16	Extrarenal	Renal blood cyst as cause	Nephrectomy	Died
Gutiérrez	1928	F, 34	Extrarenal	No cause	Drainage	Cured
Gyselynck	1910	......	Extrarenal	No cause; old organized hematoma		
Giuliani	1913	F, 52	Subcapsular	Blood cyst of kidney	Nephrectomy	Cured
Harris and Friedrichs	1922	M, 32	Extrarenal	Periarteritis nodosa	None	Died
Hawkins	1894	M, 31	Bilateral extrarenal	Aneurysm of renal artery	None	Died
Haebler	1928	F, 34	Extrarenal	Nephritis cause; scorbutus	Drainage	Cured
Hartmann	1906	......	Extrarenal	Carcinoma of kidney	Nephrectomy	Cured
Hildebrand	1895	F, 19	Extrarenal	Aneurysm of renal artery	Drainage	Cured
Hering	1912	M, 7	Extrarenal	Scarlatina cause; nephritis	Drainage	Died
Herzberg	1930	F, 89	Extrarenal	Renal tumor	Laparotomy	Died
Higgins (Fulton)	1904	F, 36	Extrarenal	Aneurysm of renal artery	None	Died
Hinz	1913	F, 56	Extrarenal	Myolipoma of kidney	Nephrectomy	Cured
Heilmann	1930	......	Extrarenal	No cause	Nephrectomy	Cured
Heilmann	1930	M, 56	Extrarenal	Arteriosclerosis	None	Died
Heilmann	1930	M, 27	Extrarenal	Sepsis	Drainage	Cured
Heilmann	1930	F, 14	Extrarenal	Scarlet fever; nephritis	None	Died
Hogge	1920	......	Subcapsular	No cause		
Hueter	1908	F, 35	Extrarenal	Nephritis	None	Died
Hullsick	1931	F, 49	Subcapsular	No cause; pararenal cyst	Nephrectomy	Cured
Ilyin (Israel)	1929	F, 38	Extrarenal	Nephritis and adenocarcinoma of kidney	Nephrectomy	Cured
James	1930	F, 36	Extrarenal	Cirrhosis of liver	Drainage	Cured
Janssen	1922	M, 28	Extrarenal	Periarteritis nodosa	Drainage	Died

TABLE 6.—*Cases Collected from the Literature* *—Continued

Author	Year	Sex; Age	Location	Cause and Pathologic Condition	Treatment	Result
Joseph...............	1908	M, 70	Extrarenal	Suppurative nephritis	Nephrectomy	Died
Joseph...	1905	M, 18	Subeapsular	Toxic nephritis	Drainage	Cured
Keen...............	1900	F, 45	Extrarenal	Aneurysm of renal artery	Nephrectomy	Cured
Kirmisson...........	1899	F, 12	Subeapsular	No cause; hematonephrosis	Drainage	Cured
Koch...............	1900	M, 31	Bilateral extrarenal	Pararenal cyst; nephritis	None	Died
Körte..............	1912	M, 57	Extrarenal	Renal cyst cause; infection	Nephrectomy	Died
Körte..............	1912	... ..	Extrarenal	Sarcoma of kidney	Nephrectomy	Cured
Krogius.............	1922	F, 67	Subeapsular	No cause; hematonephrosis; cyst; nephritis	Drainage	Cured
Krogius.............	1922	M, 55	Subeapsular	Nephritis	Drainage	Cured
Kümmell............	1914	M, 33	Extrarenal	Nephritis; sclerosed hematoma	Nephrectomy	Cured
Lancereaux..........	1868	M, 70	Subeapsular	Blood cyst of kidney	None	Died
Laux...............	1925	M, 47	Extrarenal	Periarteritis nodosa	None	Died
Lüwen..............	1912	M, 20	Extrarenal	Hemophilia	None	Died
Lüwen..............	1922	M, 49	Subeapsular	Calculus; pyelonephritis	Operation	Died
Lenk...............	1909	F, 20	Extrarenal	Nephritis	Drainage	Died
Lenk...............	1909	F, 25	Extrarenal	Nephritis cause; hydronephrosis	Nephrectomy	Cured
Leclerc-Dandoy.......	1909	M, 60	Extrarenal	Nephritis	Nephrectomy	Cured
LeComte............	1926	M, 23	Extrarenal	Hydronephrosis	Nephrectomy	Cured
Lejars and Sebileau...	1857	F, 49	Extrarenal	Suprarenal cause; renal blood cyst	Exploratory operation	Died
Lediard.............	1924	F, 49	Subeapsular	Nephritis cause; renal infection	Nephrectomy	Died
Legueu.............	1902	M, 38	Subeapsular	No cause; hematonephrosis	Nephrectomy	Cured
Leconte............	1897	......	Extrarenal	Suprarenal		
Lehnert............	1914	M, 62	Extrarenal	Arteriosclerosis as cause; nephritis	None	Died
Leopold............	1852	F, 33	Extrarenal	No cause; blood cyst of kidney	Nephrectomy	Cured
Lippens............	1913	F, 38	Extrarenal	Arteriosclerosis and nephritis cause; hematonephrosis	Nephrectomy	Cured
Lincoln............	1918	M, 64	Extrarenal	Arteriosclerosis; rupture of renal artery; nephritis	Nephrectomy	Died
Maisonneuve.........	1865	M, 57	Subeapsular	Blood cyst of kidney	Puncture	Died
Marshall............	1883	F, 13	Extrarenal	Suppurative hematoma 9 months after trauma	Drainage	Cured
Mackenzie..........	1930	M, 25	Extrarenal	Polycythemia	Nephrectomy	Cured
Malherbe...........	1890	M, 28	Extrarenal	Nephritis; hematonephrosis	Nephrectomy	Cured
Mertens............	1922	M, 21	Extrarenal	Periarteritis nodosa	Laparotomy	Died
Meyer.............	1919	M, 27	Extrarenal	Pyelonephritis; eroded artery	Nephrectomy	Cured
Meyer.............	1919	M, 42	Extrarenal	Hypernephroma	Drainage	Died
Meyer and Singer......	1927	F, 46	Extrarenal	Aneurysm of renal artery; infected renal pedicle	Nephrectomy	Cured
Michaux............	1906	M, 46	Extrarenal	Cause: aneurysm of epigastric artery; arteriosclerosis, infection	Drainage	Died
Minkowski..........	1906	M, 21	Extrarenal	Polycythemia cause; pararenal blood cyst	Drainage	Cured
Morris.............	1886	F, 38	Extrarenal	No cause; carcinoma of uterus	....	Died
Mayo Clinic.........	1927	M, 72	Subeapsular	Blood cyst of kidney	Nephrectomy	Cured
Mayo Clinic.........	1928	M, 24	Subeapsular	Blood cyst of kidney	Resection	Cured
Markley............	1909	M, 70	Extrarenal	Aneurysm of renal artery	None	Died
Miller.............	....	......	....	....	....	......
Munger............	1932	F, 54	Subeapsular	Blood cyst of kidney	Nephrectomy	Cured
Nicolich...........	1930	......	Extrarenal	Arteriosclerosis cause; thrombosis of renal vein	None	Died

TABLE 6.—*Cases Collected from the Literature* *—Continued*

Author	Year	Sex; Age	Location	Cause and Pathologic Condition	Treatment	Result
Oestreich.............	1891	F, 50	Extrarenal	Aneurysm of renal artery; arteriosclerosis	None	Died
Pauchet.............	1911	M, 55	Extrarenal	....	Drainage	Cured
Pauchet.............	1911	M, 48	Extrarenal	Infected kidney	Drainage	Died
Pick.............	1910	F, 53	Extrarenal	No cause	Drainage	Cured
Pagenstecher.........	1912	......	Extrarenal	Sarcoma of kidney	Nephrectomy	Died
Peters.............	1921	M, 58	Subcapsular	Perinephritis	Nephrectomy	Cured
Plequé.............	1898	F, 55	Extrarenal	No cause; pararenal blood cyst	Nephrectomy	Cured
Parrot.............	1872	......	Subcapsular	Suprarenal; thrombosis of renal vein	No record	
Parrot.............	1872	......	Subcapsular	Suprarenal; thrombosis of renal vein	No record	
Parrot.............	1872	......	Subcapsular	Suprarenal; thrombosis of renal vein	No record	
Prym.............	1924	F, 59	Extrarenal	Hypernephroma	Nephrectomy	Died
Prym.............	1924	F, 44	Extrarenal	Chorio-epithelioma in kidney from uterus	Hysterectomy	Died
Padtberg.............	1925	M, 54	Extrarenal	Nephritis	Laparotomy	Died
Plorry.............	1835	F, 50	Subcapsular	Renal blood cyst	None	Died
Pritchard.............	....	......	....	....	....	......
Pontick.............	....	......	....	....	....	......
Poirier.............	1888	F, 48	Subcapsular	Renal blood cyst	Puncture	Died
Rayer.............	1837	M, 75	Extrarenal	Suprarenal	None	Died
Rayer.............	1839	M, 65	Extrarenal	Suprarenal	Drainage	Cured
Rapin.............	1910	M, 55	Extrarenal	Nephritis	Drainage	Died
Recamier.............	1893	F, 59	Subcapsular	Renal blood cyst	Resection	Cured
Reinhardt.............	1918	F, 30	Extrarenal	Aneurysm of ovarian artery	None	Died
Reuss.............	1912	6 days	Extrarenal	Suprarenal	None	Died
Richardson.............	1925	M, 59	Extrarenal	No cause, aneurysm of renal artery	Nephrectomy	Cured
Rieber.............	1911	M, 42	Extrarenal	Nephritis	None	Died
Ricker.............	1911	M, 40	Extrarenal	Spinal paralysis; infarct of renal bed as cause	None	Died
Ricker.............	1911	M, 40	Extrarenal	Gallbladder disease	Cholecystectomy	Died
Ribmer.............	1916	......	Extrarenal	Suprarenal cause; typhoid		
Ritter.............	1912	M, 29	Extrarenal	Suprarenal	Drainage	Died
Rosenbach.............	1917	M, 32	Extrarenal	Hypernephroma	Nephrectomy	Died
Roth.............	1924	M, 48	Extrarenal	Nephritis and arteriosclerosis cause	None	Died
Rouppe.............	1770	......	Extrarenal	Traumatic aneurysm of renal artery	None	Died
Roussel.............	....	M, 23	....	Blood cyst of kidney	Nephrectomy	Died
Saint-Cène.............	1921	M, 35	Extrarenal	No cause	Nephrectomy	Cured
Schäfer.............	1921	M, 46	Extrarenal	Arteriosclerosis	Nephrectomy	Died
Szenes.............	1923	M, 48	Extrarenal	Nephritis and infarct	Nephrectomy	Cured
Schultze.............	1916	F, 29	Extrarenal	No cause	Drainage	Cured
Schultze.............	1916	M, 64	Extrarenal	Pyemia; perinephritis	Drainage	Died
Schlichting.............	1912	M, 28	Extrarenal	Nephritis	Drainage	Cured
Schiffmann.............	1915	F, 26	Extrarenal	Nephritis	None	Died
Schloss.............	1926	F, 41	Subcapsular	Tuberculosis of kidney	Nephrectomy	Cured
Seidel.............	1912	M, 28	Extrarenal	Nephritis	Drainage and laparotomy	Cured
Secrétan.............	1930	M, 26	Extrarenal	Hydronephrosis	Nephrectomy	Cured
Soroko.............	1927	M, 34	Extrarenal	Tumor of kidney	Nephrectomy	Cured
Speese.............	1913	M, 43	Extrarenal	Nephritis	Nephrectomy	Cured
Swan.............	1931	......	Extrarenal	Renal adenoma	Nephrectomy	Cured
Sturm.............	1930	M, 50	Extrarenal	Perinephritis; trauma	Drainage	Cured
Sturm.............	1930	M, 55	Extrarenal	Perinephritis; trauma	Drainage	Cured
Schramm.............	1925	F, 50	Extrarenal	Aneurysm of renal artery	None	Died
Sohn.............	1921	F, 64	Subcapsular	Arteriosclerosis; hematonephrosis	Drainage	Died
Sohn.............	1921	F, 54	Subcapsular	Arteriosclerosis; hydronephrosis; carcinoma of uterus	None	Died

TABLE 6.—*Cases Collected from the Literature* *—Continued*

Author	Year	Sex; Age	Location	Cause and Pathologic Condition	Treatment	Result
Singer..................	1925	F, 70	Extrarenal	Aneurysm of renal artery; arteriosclerosis	Nephrectomy	Cured
Singer..................	1923	F, 46	Extrarenal	Infection and erosion of renal artery	Nephrectomy	Cured
Schmorl.................	....	......	....	....	....	......
Schmorl.................	....	......	....	....	....	......
Siredey.................	1855	M, 23	Subcapsular	Lead poisoning; blood cyst of kidney	None	Died
Tage-Hansen..........	1918	F, 35	Extrarenal	No cause	Drainage	Cured
Trulli..................	1916	M, 66	Extrarenal	Aneurysm of renal artery	Operation	Died
Thomas (Judd)........	1917	M, 65	Extrarenal	Calcified hydronephrosis	Nephrectomy	Cured
Tschmarke.............	1929	M, 49	Extrarenal	Metastatic carcinoma of kidney	Nephrectomy	Died
Tuffler.................	1906	M, 40	Extrarenal	Sarcoma of kidney	Nephrectomy	Died
Tureo..................	1927	......	....	....	....	......
Traube.................	1571	......	....	....	....	......
Wolff..................	....	Young man	Subcapsular	Blood cyst of kidney	Nephrectomy	
Wolff..................	....	Young man	Subcapsular	Blood cyst of kidney	Nephrectomy	
Vogeler................	1922	F, 62	Extrarenal	Aneurysm of renal artery	None	Died
Wade..................	1915	M, 20	Bilateral extrarenal	Nephritis cause; syphilis and malaria	None	Died
Waegner...............	1931	M, 39	Extrarenal	Aneurysm of renal artery	Drainage	Died
Walther...............	1902	F, 22	Extrarenal	No cause; cathartic; pararenal blood cyst	Drainage	Cured
Walter.................	1921	M, 33	Bilateral extrarenal	Periarteritis nodosa	None	Died
Willis and Bonet.......	1700	Child	Extrarenal	Exanthem (infection)	None	Died
Wright.................	1931	F, 70	Extrarenal	Tumor of kidney	Nephrectomy	Cured
Wildbolz...............	....	......	....	....	....	......
Wunderlich............	1846	......	....	....	....	......
Zweig.................	1928	M, 46	Extrarenal	Arteriosclerosis	Drainage	Cured

SUMMARY

1. Seventy-six per cent of experiments on animals with ligation of the renal vein were positive for perirenal hematoma, and 100 per cent for parenchymal hemorrhage.

2. One hundred and seventy-eight assembled cases showed almost 70 per cent of renal and suprarenal disease associated with perirenal hematoma.

3. The causative disease of the kidneys, suprarenals, blood vessels and infections are all capable of sudden congestions of the organs and elevation of intrarenal tension.

4. Spontaneous perirenal hematoma may often be the result of sudden congestion of a diseased organ.

5. A case is reported which was due to an extrarenal cause.

6. Nephrectomy is the operation of choice, with renal bleeding.

7. Spontaneous cases in which no cause is discovered are probably explained by a sudden renal congestion, acting on some pathologic condition of the kidney or of the perirenal tissues. Even in the cases with a demonstrable cause, the mechanism of hemorrhage may be as suggested.

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TRANSPLANTATION OF THE INTACT MAM-MALIAN HEART

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The subject of transplantation of various tissues or organs is important, since great practical value might come from the development of a successful method. This applies particularly to the transplantation of an organ such as the kidney, whereby a normal organ might be exchanged for a diseased one. A comprehensive review of the subject of transplantation of tissue has been made recently by Loeb,[1] and we shall, therefore, mention only a few considerations which are pertinent to our report.

Two methods have been used for the transplantation of tissue. The method usually employed both clinically and experimentally has been to excise a small section of tissue and to implant it in the desired situation, expecting it to obtain its own blood supply. The other method has been to transplant a whole organ, anastomosing its blood vessels to other suitable vessels. The latter method was made technically possible by the development of vascular surgery by Carrel.[2] Owing to the claims of certain surgeons, with particular reference to implantation of sex glands and the striking success of an occasional experimental transplantation, the procedure often is considered successful. However, the results of numerous investigators have demonstrated that auto-transplantation, that is, reimplantation of tissue or of an organ in the same subject often is successful, whereas homotransplantation, that is, implantation into another subject of the same species is rarely successful, regardless of the tissue or organ transplanted.

1. Loeb, Leo: Transplantation and Individuality, Physiol. Rev. **10**:547 (Oct.) 1930.

2. Carrel, Alexis: The Surgery of Blood Vessels, Bull. Johns Hopkins Hosp. **18**:18 (Jan.) 1907.

In an investigation in which a denervated heart preparation was desirable, one of us (Dr. Markowitz) suggested that a transplanted heart might be employed. This suggestion led to the present investigation, and, although the results have not fully justified our expectations, they seem worthy of presentation as adding further data concerning transplantation of organs and as demonstrating a method that may be of value in research on the heart. It is obvious that all of our transplantations of the heart are homotransplantations. The essential procedure was to establish coronary circulation of the transplanted heart by anastomosing its aorta to a suitable vessel of the recipient. From the results of preliminary experiments which included several methods of procedure, two technical methods were developed which gave about equally successful results. With the first method, it was essential to maintain the tonus of the heart as long as possible throughout the procedure and to establish the coronary circulation by anastomosing the central end of the carotid artery to the aorta. This was accomplished by first preparing the necessary vessels of the recipient and then obtaining the heart from the donor by the judicial ligation of the larger arteries in relation to the ligation of the larger veins so that effective coronary circulation was maintained as long as possible. It was necessary to operate with speed in order to maintain the cardiac tonus and to obviate the possibility of intravascular clotting. It was found possible to transplant a heart in which the time between the cessation of the contraction of the heart and the establishment of the coronary circulation with the blood of the donor was less than five minutes. With the second method, it was essential to ligate the large veins before the large arteries, and thus prevent the possible dilatation of the heart and at the same time stop its contraction. To prevent the possibility of intravascular clotting the donor was heparinized just before operation, and the coronary circulation was established by anastomosis of the aorta to the peripheral end of the carotid artery. The details of the technic follow.

All operative procedures were carried out under ether anesthesia with rigid aseptic technic. The preparation of the field of the recipient was as follows: The carotid artery of one side, preferably the left, and the jugular vein of the opposite side were dissected free. It is convenient, but not essential, to use dogs of good size. The adventitia was carefully stripped from the vessels in the usual manner for anastomosis. The field was then packed off with moist gauze compresses. With a sharp knife these vessels were sectioned between protected clamps from 3 to 4 cm. from the suprasternal notch, and the blood was squeezed out. If the first method of transplantation was to be employed, the peripheral end of the common carotid artery was ligated while the protected clamp was applied to the central end, and the latter was prepared for anastomosis by removal of the remaining adventitia. If the second method of transplantation was to be used, the opposite was done: The peripheral end of the carotid artery was

prepared for anastomosis and the central end ligated. A similar procedure was carried out for the jugular vein, with the difference that the cephalic end of the vein was always tied, the cardiac portion being occluded with forceps. The usual three sutures of fine silk were placed equidistant in each vessel, and the whole field was covered with moist gauze. Meanwhile a small dog was etherized and maintained under artificial respiration.

If the first method of transplantation was carried out, the procedures were as follows: The thoracic cavity was entered through a left intercostal incision, and the heart was exposed. Loose ligatures were placed around the great arteries, aorta, brachiocephalic artery, left brachial artery, vena cava and azygos vein. The pericardium was then entered, and the largest branch of the pulmonary artery was located and tied. The left pulmonary veins were ligated in turn. The right branch of the pulmonary artery and the right pulmonary vein were exposed. Then, in alternate succession, the ligatures were tightened on the aorta and on the other large veins and arteries in such an order that the coronary circulation was maintained, the heart never being allowed to become overdistended. Finally, the remaining pulmonary vessels were ligated. All the vessels were then sectioned distal to the points of ligation, and the heart was removed to the previously prepared operative field of the recipient. The left branch of the pulmonary artery was anastomosed to the previously prepared central end of the right jugular vein. The clamp was removed from the jugular vein, and the blood in the heart gently squeezed out. This not only emptied the heart of blood, but permitted the deposit of fibrin around the suture line, which prevented subsequent leakage. A strong clamp, or if necessary two clamps, were placed 2 to 3 cm. from the line of section of the aorta, and the end of the aorta was prepared for anastomosis. There was no need to remove much adventitia from the aorta. This vessel, especially in young animals, is extremely friable, and should be treated with great care. If the heart was taken from a large dog it was advisable to anastomose the brachiocephalic artery instead of the aorta, as otherwise the disparity in size would be too great.

If the second method of transplantation was to be employed, the thorax and abdomen were opened in the median line. The opening of the abdomen permits freer access to thoracic contents. The incision in the thorax was made in the midsternum; a self-retaining retractor was inserted, and 100 mg. of heparin in 50 cc. of sodium chloride solution, previously boiled, was injected intravenously through the inferior vena cava. This vessel was then promptly tied and cut between ligatures close to the right auricle. The superior vena cava, the azygos vein, the brachiocephalic artery, the left brachial artery and each lobe of the lungs were tied and cut between ligatures. It was essential not to tie the root of the whole lung in one ligature as the ligature almost always slips, causing uncontrollable oozing when the heart begins to beat. A strong forceps was applied to the aorta distal to the left brachial artery, and the heart was removed by cutting this vessel and the diaphragmatic attachment of the pericardium. The pulmonary artery was identified by opening the pericardium over the right auricle, and one of the large branches was carefully freed and transected proximal to its previously placed ligature. The heart was then ready to be sutured to the previously prepared vessels of the host in the manner described. The aorta or the brachiocephalic artery was anastomosed to the peripheral end of the carotid artery, and the pulmonary artery, or a branch of it, to the central end of the jugular vein. As in all anastomoses of veins, care should be taken not to twist the jugular vein while suturing it. Following anastomosis the clamps were removed first from the vein and then from the artery. Blood was permitted

to leak from the latter for a short time in order to make sure that all the air in the length of vessel exposed for anastomosis had been expelled. This prevents coronary embolism due to the entrance of air into the coronary arteries. When it had been accomplished, the clamp was removed from the aorta and a suitable pocket was made for the organ; if the heart beat became established, the wound was closed in the usual manner.

In some experiments the pericardium was removed from the transplanted heart, and in others it was left intact. No particular difference in the length of survival was noted in the two groups of experiments. However, it was found that if the pericardium was also transplanted, a wound should be made to permit the drainage of the large amount of pericardial fluid that always forms.

The main cause for our failures was the distention of the heart with blood before its beat was established. The valves of the heart will not function if the tonus of the cardiac muscle is abolished or low. Since the new pathway for the blood was established only to take care of the coronary circulation, the blood that leaked by the insufficient valves was trapped in the cavities of the quiescent heart. Many different expedients were tried to overcome this difficulty, such as anastomosis of the vena cava of the transplanted heart to the cephalic end of the transected jugular vein, anastomosis of the vena cava to a branch of the pulmonary artery and the making of an artificial foramen ovale. None of these procedures was found to be of sufficient value to merit its employment. The main procedures found to be of value in overcoming this difficulty were: (1) restoration of the coronary circulation by using the peripheral end of the carotid artery, by which method if the pressure was sufficiently low the impaired valves would not leak; (2) temporary opening of one of the venae cava when the quiescent heart began to fill with blood in order to permit the escape of blood until the beat became established, and (3) an attempt to maintain the cardiac tonus so that a minimum of leakage occurred.

GENERAL BEHAVIOR OF THE TRANSPLANTED HEART

The heart usually begins to contract immediately after the coronary circulation is established. Occasionally only the auricles and the right ventricle beat immediately and the left ventricle does not begin to beat until a few hours later. Usually, when the animal has recovered from the anesthetic the pulsations are regular and vigorous. The wall of the right ventricle in its contraction undergoes considerable excursion. The rate of the pulsation varies, but generally on the animal's recovery from the anesthetic it is beating at the rate of from 100 to 130 per minute. In the next twelve hours the rate is surprisingly constant from moment to moment, and extrasystole is not detectable even over long

periods. The pulsations of the transplanted organs do not inconvenience the animal in any way. They can be counted by palpation, or the rate can be recorded with an electrocardiographic apparatus, direct leads from base to apex being employed. The electrocardiographic tracings appear surprisingly normal. If the animal struggles for any reason, the pulsation usually increases. In one experiment the rate rose from 120 to 132, when the animal was prevented from walking across the room. In another experiment the animal was induced to take a vigorous run about the grounds, and the pulse of the transplanted heart increased temporarily about 15 beats per minute.

In several experiments, after careful preliminary observation, the host was given intravenous injections of thyroxin. Within eighteen hours the pulse rate of the transplanted organ was appreciably increased, whereas the rate of the host's own heart was not yet affected. As has been indicated in previous papers,[3] this experiment can be interpreted as demonstrating that the tachycardia following injections of thyroxin is independent of the central nervous system, and that the part that the central nervous system plays is of an inhibitory nature, since the denervated heart was more sensitive to the accelerating influence of this drug.

In general, however, the transplanted heart was found unsuitable for this type of experiment. After from one to eight days, irregularities became apparent which made the accurate determination of the pulse rate impossible. These irregularities were soon followed by absence of pulsation in the transplanted organ or by fibrillation. The longest period of survival in our experience was eight days. The average was about four days. When the heart was removed just before it became quiescent, the left auricle was found to be filled with a clot, and the right auricle and ventricle were distended. The surface of the heart was covered with mottled areas of ecchymosis; the heart was friable on section. Histologically the heart was completely infiltrated with lymphocytes, large mononuclears and polymorphonuclears. In some instances a heart that was beating feebly at the time of removal showed few normal-appearing muscle fibers. Often edema developed around the transplanted heart in the same manner as it occurs around the homotransplanted kidney.

3. Lewis, J. K., and McEachern, Donald: Persistence of an Accelerated Rate in the Isolated Hearts and Isolated Auricles of Thyrotoxic Rabbits: Response to Iodides, Thyroxine and Epinephrine, Bull. Johns Hopkins Hosp. 48:228 (April) 1931. Priestley, J. T.; Markowitz, J., and Mann, F. C. The Tachycardia of Experimental Hyperthyroidism, Am. J. Physiol. 98:357 (Sept.) 1931. Yater, W. M.: The Tachycardia, Time Factor, Survival Period and Seat of Action of Thyroxine in the Perfused Hearts of Thyroxinized Rabbits, Am. J. Physiol. 98: 338 (Sept.) 1931.

Our observations on the transplanted heart are in general identical with those on other transplanted tissue. It appears that functioning cardiac muscle is no less resistant as a homotransplant than is the similarly transplanted kidney. Even when the heart of a small dog is transplanted into the neck of its mother, the result is the same; the transplanted organ functions well for about twenty-four hours and then becomes irregular, and, as is often the case with the transplanted kidney, function may cease suddenly. The transplanted heart may pulsate with great vigor; five minutes later pulsation may stop completely, and grossly a cause cannot be found to account for it. With regard to short experiments, we have no hesitancy in saying that the transplanted heart should be a valuable test object for the investigation of various physiologic problems. The technic should be looked on as "viviperfusion," the perfusion fluid being unchanged blood and the duration of the perfusion twenty-four hours or more. When the heart has become irregular, it can be removed aseptically without death to the host.

Although occasional failure of the transplanted organ to function was found to be due to intravascular thrombosis, this complication was unusual. As with all other transplanted organs, it was suggested that the failure of the transplanted heart to survive for more than a few days was due to the technic. Although several theoretical considerations make this criticism invalid, nevertheless some experiments were carried out for the primary purpose of minimizing trauma, to determine the length of time the coronary circulation was stopped and for other factors which might have been deleterious to the survival of the transplanted organ. In some of these experiments the heart did not cease beating, and in others it was quiescent for not more than ten minutes. The end-results of these careful experiments were the same, the longest period of survival being five days. When it is borne in mind that there is never any difficulty in preparing an autotransplant of the kidney that will survive in the neck in good condition for months, it is readily seen that the failure of the homotransplanted heart to survive is not due to the technic of transplantation but to some biologic factor which is probably identical to that which prevents survival of other homotransplanted tissues and organs.

SUMMARY

A technic for homotransplantation of the intact mammalian heart was developed. Such transplanted hearts beat vigorously for as long as from one to eight days. However, after about twenty-four hours, irregularities of the beat may develop and the heart may gradually, although sometimes suddenly, cease to function. The general behavior of such a transplanted organ as regards function, period of survival and cytologic changes is similar to that of other homotransplanted organs.

BACTERIOLOGY OF PULMONARY ABSCESS

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The clinical questions that surround the origin, the diagnosis and the treatment of pulmonary abscess are numerous. A considerable number of them may not be answered in the light of present knowledge of this condition. The answers to some of these practical and pertinent questions must come from the reciprocal orientation of the knowledge of the surgeon and the clinician with the knowledge of the specialist in correlated fields, the roentgenologist, the pathologist, the bacteriologist, and so on. These specialists have their own puzzles. With regard to the bacteriologist, it is perhaps not too much to say that pulmonary abscess, representing a mixed infection that includes a tremendous variety of bacterial types, is extremely puzzling; and it may not be too much to say that few clinical men have been able to keep up with the changing front of bacteriology, and with the status of the great number of organisms that may be found in pulmonary abscess. In fact, few bacteriologists have the right to claim such accomplishment.

In reviewing briefly the work that has been done relative to the bacteriology of pulmonary abscess, and in attempting to show wherein the work that has been done locally agrees or disagrees with reported studies, it will not be possible to touch on some points. It is, however, more important that a bacteriologic concept of the problem be gained, for several years of association with it has revealed clearly that no narrow perspective is adequate.

There are perhaps three questions which the surgeon might ask the bacteriologist, if he did not know that the bacteriologist is not able to answer them. He might first ask whether studies of the bacterial invasion reveal anything with regard to the pathogenesis of the infection. In short, does the original infection come from embolic or from aspiratory processes? He might then ask: Just what organism or organisms are responsible for the original infection, assuming the presence in the advanced abscess of a considerable secondary flora. Coming, then, to

the progress of the developed case, he might ask in just what way the progress of the disease, and the prognosis, depend on certain particular bacteria or certain groups thereof. The consideration of these questions in their logical order will perhaps constitute a reasonable approach.

The mechanism of infection is a subject concerning which there is considerable argument. Most of these arguments are the result of the idea that the original infection arises from a septic embolus, or that it arises from aspirated blood and mucus from the mouth, presumably under general anesthesia. Cutler and Hunt [1] favor the embolus theory, based on the clinical picture (sudden onset, and so on), the frequency of occurrence in the lower right lobe, the occurrence of metastases to the brain, the frequency following local anesthesia and the frequency following procedures that favor the formation of emboli. A number of cases have occurred on the twelfth day after tonsillectomy, which some consider to favor the embolus theory. Allen [2] indicated from eighty-four cases that 53 per cent followed embolus-producing procedures. There is plenty of evidence, however, showing that foreign bodies, infection of the upper respiratory tract, submersion, and so on, are predisposing factors in many cases.

Bacteriologic evidence with regard to the mechanism of infection arises from two series of observations: There have been many attempts to duplicate the infection in animals, and the study of the bacteria of pulmonary abscess reveals that in type they duplicate closely the flora of the buccal cavity.

The experimental reproduction of abscess of the lung has been accomplished, principally within the last five years, by Smith,[3] Crowe and Scarff,[4] Holman, Weidlein, Cutler and Schlueter,[5] and Joannides,[6] the latter using an admirable series of eighty-seven dogs. Some of these experiments resulted in abscesses of the lungs and a variety of other pulmonary infections, from procedures indicating an embolic origin; similar

1. Cutler, C. C., and Hunt, A. M.: Postoperative Pulmonary Complications, Arch. Int. Med. **29**:449 (April) 1922.

2. Allen, D. S.: Etiology of Abscess of the Lung, Arch. Surg. **16**:179 (Jan.) 1928.

3. Smith, D. T.: Experimental Aspiratory Abscess, Arch. Surg. **14**:231 (Jan.) 1927; Etiology of Primary Bronchiectasis, ibid. **21**:1173 (Dec.) 1930; Fusospirochetal Disease of Lungs Produced with Cultures from Vincent's Angina, J. Infect. Dis. **47**:303 (April) 1930.

4. Crowe, S. J., and Scarff, J. E.: Experimental Abscess of Lung in Dog, Arch. Surg. **16**:176 (Jan.) 1928.

5. (a) Holman, E.; Weidlein, I. F., and Schlueter, S. A.: Proc. Soc. Exper. Biol. & Med. **23**:266, 1926. (b) Schlueter, S. A.; Weidlein, I. F., and Cutler, E. C.: New York State J. Med. **26**:767, 1926. (c) Cutler, E. C., and Schlueter, S. A.: Ann. Surg. **84**:256, 1927.

6. Joannides, M.: Surg., Gynec. & Obst. **47**:449, 1928.

results have been secured by aspiration. Although the experimenter took his individual stand in accordance with the method with which he was most successful, there is nothing to indicate to the outsider that either mechanism is not possible, or even that one is more frequent than the other. From the bacteriologic standpoint, the choice of the dog is unfortunate, owing to the frequency of contaminating flora in the healthy tissues. Furthermore, the artificial production of septic emboli, or the trapping of infected material in the bronchi, has been accomplished with material that does not reveal a clear bacteriologic picture. The most successful experiments have been accomplished by the use of purulent material from a pulmonary abscess as such, by the use of pus from the groin of a guinea-pig previously infected with abscess material, or by the use of material from the buccal cavity, from the tonsils, from pockets of pyorrhea, from lesions of ulcerative stomatitis and the like. Cutler and Schlueter [5c] performed some experiments with bacteriologically specific emboli, and secured fair results with Staphylococcus aureus, Bacterium coli and nonhemolytic streptococci. The pneumococcus failed to induce abscesses. Mr. Goldman, of our group, injected a mixture of Bacillus melaninogenicum and a few contaminating cocci intratracheally into rabbits. The organism named is one described by Oliver and Wherry in 1921; it is a very small, short, gram-negative rod, growing anaerobically on human blood agar, on which it forms a dense black pigment. Varney [7] encountered it in a number of cases of pulmonary abscess; Cohen [8] noted the organism in fourteen of sixteen cases, and we have successfully demonstrated it in more than half the specimens examined. Varney attributed to it the rôle of a significant secondary invader. Its presence in the normal mouth and elsewhere renders somewhat difficult a decision as to its particular significance. Goldman, however, succeeded in inducing a pulmonary infection from which histologic sections gave some evidence of early abscess formation.

That the bacterial flora of material from the well developed abscess is very similar to that of the buccal cavity, particularly of the unhygienic buccal cavity, may be considered as established. Briefly, the flora may consist frequently of fusiform bacilli and spirochetes, of diphtheroids, of B. melaninogenicum, of staphylococci, of all types of streptococci, of organisms of the colon group (B. coli, Proteus vulgaris), of the so-called streptothrices or filamentous types, of Micrococcus tetragenus, of pneumococci, and of gram-negative diplococci of the Neisseria group. Any or all of these may be found in the sputum, together with other organisms less frequently encountered or not easily identified. Any or all

7. Varney, P. L.: Bacterial Flora of Treated and Untreated Abscesses of Lung, Arch. Surg. **19**:1602 (Dec.) 1929.

8. Cohen, J.: Bacteriology of Abscess of Lung and Methods for Its Study, Arch. Surg. **24**:171 (Feb.) 1932.

appear with considerable frequency in specimens from pulmonary abscess. Furthermore, checking the results of our studies of specimens of sputum against the bacteriologic picture of other specimens, it seems probable that the flora of the abscess proper is similar qualitatively to that of the sputum—that is, specimens of sputum even carefully taken reveal a heavy buccal contamination, considered to be contamination for the reason that a bronchoscopic or a surgical specimen reveals similar organisms, but perhaps not so many of some varieties, or it reveals no pneumococci, or no Neisseria. Specimens of sputum should on this basis be avoided whenever possible.

Analysis of the bacteriologic evidence pertinent to the mechanism of infection would seem to indicate that the origin may well be either embolic or aspiratory, and one should probably add the abscess which is induced by pneumonias or other conditions in which it is not possible to be sure that the origin is embolic, lymphatic or otherwise. The flora of pulmonary abscess makes it difficult to picture a septic embolus, particularly, let us say, from a laparotomy, which is contaminated with anything like the organisms found in the advanced stages of the disease. However, it is not necessary to assume that the primary infection is complicated, and it seems virtually unequivocal that the heavy secondary infection which must be postulated arises from the buccal cavity. In other words, not only is it unnecessary to assume either an embolic or an aspiratory origin, but it is somewhat illogical to insist on a single route to the parenchyma of the lung.

In passing on to the next question, it should be pointed out that the two possible approaches to this question as it stands at present seem to be through intimate pathologic study at autopsy and animal experimentation. In the latter, the work which has been done is barely preliminary, and subsequent work, if it is to be enlightening, must be vastly more carefully controlled than has been possible heretofore. Incidentally, speaking as a bacteriologist, it would seem necessary to carry out this approach with better bacteriology than has been the case in most of the experiments that have been performed, at least if any conclusions are to be drawn with regard to the bacteriology of pulmonary abscess.

The question of the specific etiology of pulmonary abscess may be handled briefly. In the literature on the subject, few have ventured to suggest a specific etiologic agent. The suggestions which are made, usually regarding the fusiform bacillus, the spirochetes or a combination of the two, are not made unequivocally. They are speculative opinions. It is possible only to point out the most logical bacteriologic stand in the matter. One may assume that the truly localized abscess, of embolic or bronchiogenic origin, starts with a minor lesion in the parenchyma of the lungs. Presumably this lesion originates as an infection, and at the outset there are no clinical symptoms. Furthermore, it is not possible

to sample the lesion, provided its presence and location were known. Considering the number of suppurative conditions and the number of pyogenic organisms—considering, for a specific example, the number of organisms that may be responsible for various pneumonias—there seems to be no reason for supposing that any one organism is invariably responsible for pulmonary abscess. It is most logical to assume that a number of organisms, singly or in combination, may be responsible for the original infection. It seems virtually impossible to approach this matter seeking a plausible answer except under the rare circumstances in which a pathologically proved abscess is noted and studied immediately after death, an abscess that is in its very early stages. To be sure, the development of the early abscess may be in part determined by the nature of the original infection; it will also be determined by the location and many other factors. Thus, with regard to the specific bacteriology of this question, three points might be emphasized: First, discussions with regard to the specific initial infection rest on very uncertain data; second, the most logical assumption or postulate is that a number of organisms may be involved, not the same in different cases, and third, since the clinical abscess represents an advanced stage, heavily infested with secondary invaders, it is probable that the original infecting agent has no clinical significance.

With regard to the third bacteriologic question, concerning the relationship of the clinical development of pulmonary abscess to the bacteriology, it is likely that much more will be said in the next few years. It is clear that the unsolved clinical questions are numerous. The most casual bacteriologic study reveals that the bacteriology of the disease is very complex. At the present time, most of the studies made have been unilateral, with little attempt to correlate specifically the actual flora of the abscess with the actual clinical progress. The status of the bacteriologic questions will be clarified by a specific consideration of some of the leading organisms.

The organisms most frequently discussed are Plaut-Vincent's organisms, the fusiform bacillus and the associated spirochetes. Smith,[3] whose work has been considerable, adds to these as usually present vibrio forms and cocci. Varney [7] makes quite a bit of the black pigment-producing anaerobe which, when sought, is frequently encountered. Ermatinger,[9] in 1928, segregated the cases studied into those of pulmonary abscess, bronchiectatic abscess and bronchiectasis. Hemolytic stapylococci were most commonly found, organisms of the genus Neisseria next, and commonly hemolytic streptococci. Pneumococci, Friedländer's bacillus, diphtheroid types, Proteus and others were noted. Cohen [8]

9. Ermatinger, L. H.: Microorganisms of Lung Abscess and Bronchiectasis, J. Infect. Dis. **43**:391 (Nov.) 1928.

called attention to a group of anaerobes described in connection with pulmonary gangrene in 1898, Bacillus ramosus, Bacillus fureosus, Bacillus thetoides and others which, as he correctly stated, have been ignored in the literature for some years. It is obvious from these and other studies that there may be found in specimens from pulmonary abscess rods, cocci and spirochetes, both aerobic and anaerobic. To list all the organisms that have been found would be beside the purpose, and it would be an injustice to those organisms that have not been identified. Importance is, for example, attached to members of the genus Leptothrix by some. A case recently encountered in San Francisco yielded a number of Pseudomonas pyocyanea, very likely of significance in the case, but rarely noted in other cases.

Considerable care is needed in the interpretation of bacteriologic results in connection with the specimen examined. Specimens come from sputum, from bronchoscopy, from lobectomy, from drainage, and so on. Since the flora of the abscess is to some extent duplicated in the flora of the buccal cavity, the specimen of sputum is at least confusing. A tabulation of the cases studied locally reveals that sputums examined yielded consistently greater numbers of organisms which may or may not have been present in the abscess. The pneumococcus, for example, based on comparison of the type of specimen examined, would seem to come from the buccal cavity in many of the cases in which it is found.

Passing on to the present status and the possible rôle of specific organisms, the fusiform bacillus and the spirochetes are frequently mentioned.

The status of the fusiform bacillus is somewhat as follows: Knorr,[10] Krumwiede and Pratt,[11] Tunnicliff [12] and many others have cultivated fusiform bacilli. Those who have studied these organisms as such agree that there are three or more types. However, the types are usually noted on simple morphologic grounds, a basis of differentiation that is notoriously unsatisfactory. Those who have made intimate morphologic studies go so far as to claim that giant cocci or spirilla may arise from fusiform rods.[13] One does not have to accept or to deny these radical conceptions to acknowledge the paucity of information regarding the organisms, or the necessity for having a reasonably firm background before attempting correlation with the pulmonary abscess. From the standpoint of comparative pathology, one may say that the organisms are often encountered in the mouth, ordinarily associated with gangre-

10. Knorr, M.: Centralbl. f. Bakt. (Abt. 1) **87**:536, 1921-1922; **89**:4, 1922-1923.

11. Krumwiede, C., and Pratt, J.: J. Infect. Dis. **12**:199, 1913; **13**:438, 1913.

12. Tunnicliff, R.: J. Infect. Dis. **3**:148, 1906.

13. Mellon, R. R.: J. Bact. **4**:505, 1919; New York State J. Med. **20**:187, 1920.

nous processes. Material containing the organisms, in association with spirochetes and unknown organisms, produces localized abscesses in the groins of guinea-pigs, and has induced pulmonary abscess. This knowledge is, however, unproved as to its specific relationships, and it seems likely that Cruikshank and Cruikshank [14] are correct in saying: "It is more probable that B. fusiformis is a secondary invader of tissues already diseased or devitalized. There seems little doubt that the organism helps to maintain or further the progress of ulcerative and gangrenous conditions."

The situation with regard to spirochetes also needs clarification. These organisms should not be confused with spirilla, but the literature is difficult to interpret on any basis other than that of confused terms. Spirochetes are wavy filaments, with varying numbers of curves and varying helicine morphology, motile and varying in size in defined species. The type that is most often associated with fusiform bacilli, Treponema vincenti, may or may not be identical with Treponema buccale. Few investigators are qualified to make the finer morphologic differentiations of the four or five types of oral spirochetes, if indeed such differentiation is adequate. Noguchi was well aware of the frequent association of spirochetes in pulmonary infection, and he was well qualified to differentiate types of spirochetes, yet his final publication treats the subject as being "a very complex one because of the simultaneous presence of all of these organisms." [15] We have thus expert opinion to the effect that there are various types of fusiform bacilli and various types of spirochetes, and to pool them for purposes of simplicity is most certainly unscientific. Granting that slow scientific results must, for the moment, be passed if a clinical advantage may otherwise be gained, it must still be shown, in those cases in which these organisms are found, either fusiform bacilli or spirochetes or both, that the organisms as a group are all invasive in gangrenous processes. Much more might be said about the spirochetes, and their relationship to fusiform bacilli, but let us consider another type of organism.

Diphtheroids are very frequently encountered in specimens from pulmonary abscess. To the uninitiated, this might seem significant. Diphtheroids, however, have no bacteriologic status whatever, and certainly no clinical status. They are usually differentiated morphologically, and the criteria differ, depending on the examiner. If one is to believe the present concepts of pleomorphism of bacteria, diphtheroids have been produced from tubercle bacilli, and they have been produced from

14. Cruikshank and Cruikshank, in Bensted, H. J., and others: A System of Bacteriology in Relation to Medicine, London, His Majesty's Stationery Office, 1929, vol. 8.

15. Noguchi, H., in Jordan, E. O., and Falk, I. S.: Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928.

streptococci. In the light of present knowledge, it is as logical to suppose, perhaps, that the diphtheroids of the abscess are variants from other organisms as that they constitute a specific group with specific properties. And, if the latter more conservative view is held, what are those properties?

No significance is usually attached to organisms of the genus Neisseria, those gram-negative diplococci common to the nose and throat and frequently noted in pulmonary abscess. These organisms have specific characteristics, and may be cultivated, and the probability is that the environment of the abscess is favorable to their existence as commensals.

All types of streptococci have, at some time or other, been noted in pulmonary abscesses, speaking in general terms. The order of frequency is not certain, but the nonhemolytic type seems to head the list. That streptococci growing anaerobically are encountered is stated in various reports, and they were noted in local specimens. The evidence that these organisms are purely anaerobic is not convincing. Furthermore, the literature concerning them makes it impossible to state that there is a group of anaerobic streptococci which are purely anaerobic and which, hence, might be endowed with special capabilities in the production of necrotic processes.

One might expect the most significant organisms to be of the anaerobic types. In this field, only one of the Clostridium group, Cl. cochlearium, has apparently been recorded.[8] None of this group was found in local specimens, and Cohen found this one but once. Thus one may apparently rule out for the most part those anaerobes encountered in gas gangrene and similar infections. The black pigment-producing organism is relatively new, and its pathogenic rôle is uncertain. The work of Goldman, in connection with local cases, confirms the reports, first, that the organism is common in specimens from pulmonary abscess, and second that it is difficult to isolate, although cultivation is relatively simple. This makes clear the reasons for the slow progress in assigning a definite rôle to the organism in the pathogenesis of infection, for, if active at all, it presumably requires association with other organisms, notably cocci. The anaerobes noted by Cohen, apparently not considered to date by anyone else, were not found regularly by him. It is quite possible that one or more of them might be present in a significant number of cases, and that this occurrence might have clinical weight. Pulmonary abscess is, in a sense, localized gangrene. It is accompanied by those signs which one associates with anaerobic organisms. That these organisms, vastly different in any characteristic that one might name except oxygen requirements, may be particularly important is claimed by some; but there seems to be little thus far to substantiate the hypothesis that this broad generalization necessarily obtains in pulmonary abscess, at least.

These brief sketches leave many stones unturned. Gram-negative rods, sometimes identified as B. coli or P. vulgaris, are not uncommon in specimens studied. King and Morgan,[16] two years ago, described a case in which Proteus was apparently responsible for multiple pulmonary abscesses. Pfeiffer's bacillus and Friedländer's bacillus,[17] and others encountered occasionally, are organisms known to have pathogenic significance under proper circumstances. The filamentous organisms, bordering on Actinomyces in type, constitute a group concerning which little is known fundamentally. Definite fungi and even amebas[18] no doubt account for rare abscesses, but it seems probable that these cases would have recognized features.

The demonstration of the clinical development of a case as correlated with the bacteriology is not yet possible. One author[19] stated that a more acute disease might possibly be expected in the presence of considerable numbers of streptococci. An analysis of the cases studied in San Francisco to date indicates that, in several cases, marked clinical differences may be associated with bacteriologic differences. What these differences are only further study will tell. Whether they will correlate with clinical development is also still an open question.

To define the possible approaches to a study of this nature would take as long as a comprehensive discussion of all the organisms involved, and not because the story would be the same. All sorts of schemes have been suggested—skin tests, phagocytic tests, serologic examination, blood cultures, innumerable experimental tests, and so on. No one knows what might be revealed, but in such a problem it is essential that one stand squarely. Many studies reveal a tendency to attempt to jump a fearful number of hurdles in the chance that one might, after all, cross the tape unscathed at the other end. The answer to so complicated an infection as pulmonary abscess is probably twenty years off rather than two, at least so far as the bacteriology is concerned.

By way of a summary, hope is expressed that two points may at least stand out. It is hoped that pulmonary abscess may be bacteriologically pictured as originating from an uncertain agent but ending in the clinical picture that includes a terrific secondary invasion of numbers of organisms of various and numerous types. And it is further hoped that surgeons may gain some slight insight into the bacteriologic questions per se that are involved. These questions are related directly to the clinical questions, could a reciprocal point of view but be obtained. It may perhaps be granted that an excellent clinician may have lost touch

16. King, M. J., and Morgan, R. H.:   Am. Rev. Tuberc. **19**:182, 1929.

17. Graham, E. A.:   S. Clin. North America **2**:1501, 1922.

18. Cabbé, M.:   Bull. et mém. Soc. méd. d. hôp. de Paris **54**:373, 1930.

19. Bucher, C. J.:   Am. J. M. Sc. **179**:406, 1930.

with much in bacteriology, and it will probably be readily granted that the bacteriologist finds it difficult to get a clinical point of view. Be that as it may, the problem is objective, not subjective; it involves both good clinical work and good bacteriology.

The authors are indebted to the clinical and bacteriologic members of the local group engaged in this problem. The entire group owes a great deal to Dr. Selling Brill, whose activity and enthusiasm was responsible for the organization of the study, and whose untimely death, in January, 1932, is a loss to the group and to the surgical profession.

GASTRIC SECRETION

III. INCREASED ACID SECRETION IN A TRANSPLANTED GASTRIC POUCH DURING LACTATION

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In four dogs with transplanted gastric pouches unusual phenomena were observed during lactation. The preparation and character of these pouches have been described in detail in two previous papers.[1] In brief, the operation was done in two stages. In the first, a portion of the body along the greater curvature was cut away from the stomach and then sutured to form a pouch. This pouch was transplanted to a space in the subcutaneous tissues. The gastric blood supply to the pouch was left intact. At a second operation from three weeks to several months later, these vessels were severed, leaving the pouch dependent on a new blood supply from the abdominal wall. A second type of pouch consisted only of mucous membrane and submucosa, the muscular coats, including the plexus of Auerbach, having been removed. The secretion of these pouches has already been reported in the papers mentioned.[1]

In the four dogs described in this paper, the first two had pouches of the first type. In the third, a pouch of the first type was prepared, but the second stage had not been performed when the dog gave birth to puppies. The gastric blood supply was therefore intact during lactation. In the fourth dog, a pouch of the second type was prepared.

In the first dog, L., the pouch was prepared on April 9, 1928, and tests for secretion showed results similar to those already reported. The second stage of the operation, that is, the severing of the gastric blood vessels, had not yet been performed when, five weeks after the first stage, I left on my vacation. On my return, I found that the pouch had turned itself inside out through its opening, and that there was on the abdominal wall a protruding mass covered with mucous membrane. At an operation three months after the first procedure, the mass was reinverted and the pouch reestablished. It was placed in a space in the subcutaneous tissues. A small opening was left to form a fistula for

1. (a) Klein, E., and Arnheim, E.: Gastric Secretion: I. A Transplanted Subcutaneous Gastric Pouch, Arch. Surg. 25:433 (Sept.) 1932. (b) Klein, E.: Gastric Secretion: II. Studies in a Transplanted Gastric Pouch Without Auerbach's Plexus, ibid. 25:442 (Sept.) 1932.

the collection of gastric juice. This fistula closed spontaneously, and very little secretion could be obtained from the pouch. It would slowly fill up and form a mass under the skin the size of a small egg. On puncture about every three weeks, a thick mucus with no acid was obtained. The dog then became pregnant. No change was noted during pregnancy. Four months after the second operation, six puppies were born. Three days later the pouch opened spontaneously, and a small erosion of the skin formed at the mouth of the fistula. One week after the puppies were born, free acid could be demonstrated following the feeding of meat (table 1). The erosion and the fistula gradually increased in size and reached their maximum from four to five weeks after parturition, when the erosion was about 4 by 5 cm. in area and from 1.5 to 2 cm. deep. A test (table 1) made at this time (Dec. 18,

TABLE 1.—*Dog L., with Transplanted Subcutaneous Gastric Pouch. Fed 200 Gm. of Meat at the Beginning of the First Hour* *

Hour	Volume of Juice, Cc.	Free Hydro- chloric Acid	Total Acid
11/30/2S—One Week After Parturition			
1	0.1	..	..
2	0.6	50	83
3	1.0	25	50
4	0.8	10	33
12/18/2S—During Lactation, About Four Weeks After Parturition			
1	2.2	88	105
2	1.3	85	100
3	1.4	82	93
4	1.1	77	86

* Gastric juice collected each hour from the fistula. In this and in all the succeeding tests free and total acid were determined by titration against tenth-normal sodium hydroxide with Toepfer's reagent and with phenolphthalein.

1928) with 200 Gm. of meat showed that the quantity of secretion had increased and that the free acid was markedly increased. The quantities of secretion varied in the succeeding tests, but remained around this level for about four weeks (about two months after parturition) and then diminished, although the free acid did not again disappear. The erosion progressively diminished in size, and three months after the puppies were born it was healed. The fistula, however, remained open.

The striking points observed were:

1. The reappearance during lactation of free acid secretion in a pouch that had been secreting only small quantities of mucus during pregnancy and before that time.

2. The digestion of the skin and subcutaneous tissues over a very wide area, even though the secretion was small in quantity.

3. The healing of the erosion at the end of lactation.

4. The drop in the quantity and acidity of the secretion after the end of lactation, although the sac did not revert to its old state. Secretion of free acid persisted.

In a second dog, F., in which a similar subcutaneous gastric pouch had been prepared (Jan. 8, 1929), the secretion had markedly diminished after the second stage of the operation, which consisted in severing the gastric blood vessels. It was then noted that the dog was pregnant. During the pregnancy there was no apparent increase in the secretion, as is shown in table 2 (March 19), taken nine days before the birth of seven puppies.

During pregnancy there had been no erosion around the mouth of the fistula. During lactation erosión began to take place, so that four weeks later there was extensive digestion of the skin and subcutaneous tissues over an area 5 by 7 cm. The results of a test for secretion done

TABLE 2.—*Dog F., with Transplanted Subcutaneous Gastric Pouch. Fed 200 Gm. of Meat at the Beginning of the First Hour*

Hour	Volume of Juice, Ce.	Free Hydro-chloric Acid	Total Acid
3/19/29—Nine Days Before Birth of Puppies			
1.	0.2	0	..
2.	0.2	0	..
3.	0.2	Trace	..
4.	0.4	25	50
4/25/29—During Lactation, About Four Weeks After Parturition			
1.	1.0	30	70
2.	1.5	53	86
3.	1.0	70	100
4.	0.7	57	85

at this time are shown in table 2 (April 25). This table shows a fairly marked increase in the secretion and a decided increase in the free acid and total acid. The secretion gradually subsided, so that two months later it was down to the level it had been before lactation and the erosion had healed. The same phenomena were repeated in two subsequent pregnancies and lactations.

The third dog, N., was operated on April 16, 1929. A gastric pouch containing all the coats was transplanted into the subcutaneous tissues of the abdominal wall. On May 13, a test for secretion showed the results presented in table 3. At this time the original gastric vessels to the pouch had not yet been severed. On May 25, five puppies were born. A test on June 5 gave the results presented in table 3. The amount of the secretion and the acidity are markedly increased. The erosion around the opening of the fistula became very pronounced, just as in the first two dogs. On August 14, a little over two and one-half months after the puppies were born, the secretion had dropped to the

figures shown in table 3, and the erosion was practically healed. The important point to remember in this dog is that the gastric blood supply had not been severed at the time of lactation.

In the fourth dog, B., on Oct. 10, 1930, a transplanted pouch was prepared from mucous membrane and submucosa. This pouch was also made from the body of the stomach, but the wall of the pouch consisted of the mucous membrane and submucosa only. It was the first time an attempt was made to prepare this kind of a pouch, and perhaps the technic was not as good as that later developed. At any rate, the pouch gave very little secretion. The secretion consisted chiefly of mucus, but free hydrochloric acid could be demonstrated in it by Congo paper. The quantities were so small that adequate tests could not be performed.

TABLE 3.—*Dog N., with Transplanted Subcutaneous Gastric Pouch. Fed 200 Gm. of Meat at the Beginning of the First Hour. Gastric Vessels to This Pouch Intact*

Hour	Volume of Juice, Cc.	Free Hydro-chloric Acid	Total Acid
5/13/29—Twelve Days Before the Birth of Puppies			
1	2.3	65	104
2	3.9	87	135
3	3.6	96	115
4	4.3	113	132
6/5/29—During Lactation, Eleven Days After Parturition			
1	4.5	104	122
2	8.0	118	136
3	9.7	130	144
4	8.5	146	158
8/14/29—About Two and One-Half Months After Parturition			
1	0.2	...	...
2	1.4	86	102
3	2.8	72	94
4	4.6	80	86
5	3.5	88	104

On December 26, four puppies were born. The puppies died soon after birth, so that there was no period of lactation. The quantities of secretion in the pouch did not increase, nor did any erosion appear around the fistula. On Jan. 9, 1931, the vessels to the pouch were cut, leaving it dependent on the abdominal wall for blood supply. The pouch secreted only a little mucus, and the opening was frequently dilated, but it often closed in spite of this. On June 6, during a state of pregnancy, the pouch was incised (the opening had closed) and found to contain mucus with free hydrochloric acid (35 cc. of tenth-normal solution). On June 23, a test for secretion was performed (table 4). This was the first time that enough secretion followed the ingestion of food to permit a consecutive test. Three days later five puppies were born. On July 5, the skin began to break down around the fistula. By July 15, the digested area was 4 by 6 cm. and extended through the skin and subcutaneous tissues. A test was done on July 2, one week after parturi-

tion (table 4). It showed a marked increase in secretion and an increase in concentration of the free and total acid. On August 13, the free acid had disappeared (table 4) and the quantity had diminished. The erosion was healed.

The important points are:

1. No increase of secretion during the first pregnancy and after it. There was no period of lactation owing to the death of the puppies.

2. Secretion in measurable amounts starting near the end of the second pregnancy. It had been present only in exceedingly small amounts before.

TABLE 4.—*Dog B., with Transplanted Subcutaneous Gastric Pouch Consisting of Mucous Membrane and Submucosa. Fed 200 Gm. of Meat at the End of the First Hour*

Hour	Volume of Juice, Cc.	Free Hydro-chloric Acid	Total Acid	Total Chlorides
6/23/31—Three Days Before Birth of Puppies				
1.	0.2	20	55	...
Fed 200 Gm. of meat				
2.	0.7	35	85	144
3.	0.6	25	60	...
4.	0.4	15	60	148
5.	0.6	25	55	...
7/2/31—During Lactation, One Week After Parturition, Shows Marked Increase of Secretion				
1.	0.7	0	80	...
Fed 200 Gm. of meat				
2.	2.9	50	80	146
3.	2.4	60	90	144
4.	0.7	70	90	...
5.	1.9	60	85	148
6.	2.3	70	95	146
8/13/31—Six and One-Half Weeks After Birth of Puppies				
1.	0	..	..	...
Fed 200 Gm. of meat				
2.	0.45	0	45	...
3.	0.75	0	50	...
4.	0.60	0	60	...
5.	0.30	0	50	...
6.	0.25	0	55	...

3. A marked increase of secretion during the lactation following the second pregnancy, both in quantity and in concentration of free and total acid.

4. During lactation, the appearance, for the first time, of erosion of the skin and subcutaneous tissues around the mouth of the fistula.

5. After lactation, the disappearance of the response of free acid to food and the healing of the erosion.

COMMENT

The striking facts are: (1) the appearance of gastric secretion in transplanted pouches during lactation and (2) the marked erosion of the abdominal wall and the opening of the fistula.

The Appearance of Acid Secretion During Lactation.—In the first dog there was no secretion until lactation started. In the second and third dogs, secretion was present before and during pregnancy, but a marked increase of secretion took place only during lactation. In the second dog the same phenomena occurred during three periods of lactation. In the fourth dog secretion began near the very end of pregnancy and reached its maximum during lactation. In a previous pregnancy followed by death of the puppies there had been no lactation and no increase of secretion. In the fourth dog too the transplanted pouch consisted of mucous membrane and submucosa only.

Ivy and Farrell,[2] working with pouches similar to those of the first two dogs, reported that the secretion during pregnancy and lactation was increased 25 per cent. The results reported in the foregoing dogs differ from theirs in that the increased secretion occurred during lactation.

This increase of secretion may be explained in two ways. The first is the marked dilatation of the blood vessels in the abdominal wall accompanying lactation and the resultant increase of the blood supply.

It has previously been noted [1a] that following the second stage of the preparation of these pouches there is a drop in the quantity and acidity of the secretion. This stage consists, as stated, in section of the original gastric blood vessels, leaving the pouch dependent on the abdominal wall. The drop in secretion was thought most probably to be due to the sudden diminution in the blood supply. It is, of course, possible that in the foregoing dogs the opposite condition was present, and that the dilatation of the blood vessels of the abdominal wall and the increased blood supply permit the increased secretion. However, though this occurrence may be responsible in part, further consideration leads to the view that other factors are involved.

The literature does not give much information concerning the effect of blood supply on gastric secretion. Several years ago, Lim, Ivy and McCarthy [3] advanced a working hypothesis that gastric secretion was dependent on increased blood supply, but this was before they were convinced that a humoral stimulant existed for the secondary phase. Their results may be explained on the latter basis.

Some time ago, while seeking a simple method to produce anacidity, I experimented with a diminished blood supply to the body and fundus.

2. Ivy, A. C., and Farrell, J. I.: Contributions to the Physiology of Gastric Secretion: VIII. Proof of Humoral Mechanism, New Procedure for Study of Gastric Physiology, Am. J. Physiol. **74**:639, 1925.

3. Lim, R. K. S.; Ivy, A. C., and McCarthy, I. E.: Contributions to the Physiology of Gastric Secretion by Local (Mechanical) and Chemical Stimulation, Quart. J. Exper. Physiol. **15**:13 and 55, 1925.

These experiments have not been reported. The idea was to diminish both the amount of blood which carried the necessary materials for the production of hydrochloric acid and, at the same time, the amount of the humoral stimulant responsible for the second phase of gastric secretion. The gastric artery, all the vasa brevia and the epiploica sinistra were tied. Thus the body and fundus could receive blood only through the branches anastomosing with the pyloric arteries and the epiploica dextra. No gangrene of the wall of the stomach ever followed this procedure. Evidently sufficient blood supply to prevent such a sequel reached the affected parts through collateral channels. In the tests, the gastric contents were aspirated every twenty minutes through a long no. 20 French catheter that was inserted into the stomach after feeding

TABLE 5.—*Gastric Secretion Before and After Ligation of the Gastric Artery, the Vasa Brevia and the Epiploica Sinistra* *

Time		Free Acid	Total Acid
	Before Ligation of Vessels		
20 min		0	25
40 min		0	30
1 hr		0	45
1 hr. 20 min		10	55
1 hr. 40 min		25	75
2 hr		45	90
2 hr. 20 min		40	90
	After Ligation of Vessels		
20 min		0	20
40 min		0	25
1 hr		0	35
1 hr. 20 min		0	45
1 hr. 40 min		25	70
2 hr		35	80
2 hr. 20 min		35	75

* Secretion was obtained by aspirating every twenty minutes through a catheter left in place (see text) following a meal of 200 Gm. of meat and 150 cc. of fresh salt-free broth.

the dogs 200 Gm. of meat and 150 cc. of salt-free fresh broth. The catheter was left in situ and brought out through a space between two teeth. A specially constructed muzzle prevented the dog from biting the catheter. After closure of the blood vessels mentioned, the concentration of the hydrochloric acid in the stomach was only moderately reduced (table 5). If, in addition, the left vagus was cut just below the diaphragm, there was a more marked change. Section of both vagi [4] and ligature of the vessels usually caused an anacidity (table 6), but free hydrochloric acid could occasionally be demonstrated. These tests gave information only as to the concentration of acid in the stomach, and not as to the actual quantity of the secretion. In all cases (even without section of the vagi) there was a tremendous dilatation of the

4. The purpose of sectioning the vagi was to eliminate the psychic phase in addition to the secondary phase, the elimination of which had been attempted by the vessel ligation.

body and fundus of the stomach to four or five times the normal size. There was also a marked stasis of food, so that dogs killed eight hours after a meal showed enormous stomachs full of food—much more than was taken at the last meal. It was therefore evident that the method was not feasible clinically for the lowering of acidity.

In summarizing the facts concerning the blood supply, it may be said that (1) it is possible that the increased secretion during lactation is due in part, at any rate, to the increased blood supply, but that (2) no definite experimental evidence has been found that increased circu-

Table 6.—*Gastric Secretion Before and After Intra-Abdominal Section of Both Vagi at Level of Diaphragm and Ligation of the Gastric Artery, the Vasa Brevia and the Epiploica Sinistra* *

Time	Free Acid	Total Acid	Pepsin†	Total Chlorides‡
Before Section of Vagi and Ligation of Vessels				
20 min.	0	25	...	...
40 min.	0	35	64	140
1 hr.	0	30	...	...
1 hr. 20 min.	0	35	...	...
1 hr. 40 min.	0	40	100	144
2 hr.	35	85	...	...
2 hr. 20 min.	50	110	...	...
2 hr. 40 min.	40	90	144	156
3 hr.	30	100	...	...
3 hr. 20 min.	50	110	288	158
After Section of Vagi and Ligation of Vessels				
20 min.	.0	10	64	...
40 min.	0	10	...	142
1 hr.	0	20	...	...
1 hr. 20 min.	0	25	100	142
1 hr. 40 min.	0	20	...	...
2 hr.	0	20	256	140
2 hr. 20 min.	0	25	...	...
2 hr. 40 min.	0	20	228	148
3 hr.	0	25	...	...

* Secretion was obtained by aspirating every twenty minutes through a catheter left in place (see text) following a meal of 200 Gm. of meat and 150 cc. of fresh salt-free broth.
† Pepsin is expressed in Mett units. Total chlorides are expressed as cubic centimeters of tenth-normal solution.

lation produces such an effect and that (3) markedly diminishing the blood supply of the whole stomach only moderately affects the secretion.

Much experience with normal and pathologic gastric secretion has left the feeling that the so-called primary and secondary phases as they are known may not tell the whole story of the secretion. For instance, removal of even three fourths of the stomach, especially in intractable cases of ulcer, can still leave the patient with hyperacidity, although in the large majority of cases a hypo-acidity or an anacidity is produced. Some variation exists in the secreting mechanism of these persons. Any facts, therefore, suggesting leads as to further possible factors influencing secretion deserve careful consideration. For that reason due weight has been given the hypothesis that an increased blood supply

may be responsible for the foregoing phenomena. Yet this explanation does not seem to be entirely adequate, and one is justified in seeking an additional cause.

One would naturally turn next to the state of lactation itself. There are two sets of observations that prompt one to do this. In the first place, in the third dog the pouch was still supplied by its normal gastric vessels and was not dependent on the abdominal wall for its blood supply. It is unlikely that these gastric vessels supplied more blood during lactation. But, of course, it may still be argued that the blood vessels of the abdominal wall dilated and thus furnished additional blood. This seems less likely in view of the finding of Hollander,[5] who had a dog with a Pavlov pouch in which he noticed that the secretion increased only during lactation and not during pregnancy. Pavlov pouches are intra-abdominal, and the normal gastric blood and nerve supply are not disturbed. It is difficult to see how an increased blood supply could have operated in this case. One is further justified in concluding that the responsible factors for this increase of secretion act through the blood stream, as the transplanted pouch in the fourth dog consisted only of mucous membrane and submucosa. All the gastric blood supply, the vagus, the sympathetics and the intrinsic myenteric plexus had been eliminated. Only blood vessels of the peripheral abdominal wall supplied it.

Though one is apparently justified, then, in seeking an additional cause, in the present state of knowledge it is hard to say what factors associated with lactation may be responsible for the increase of gastric secretion. One naturally turns to the cause of lactation. Corner [6] has recently contributed evidence to show that this is due to a secretion from the anterior pituitary gland. No facts are as yet available to show whether the latter influences gastric secretion. The work of Cushing [7] showing the stimulating effects of posterior pituitary extract on the vagus system should also be mentioned. Whether during lactation an increase of the posterior pituitary secretion accompanies the increased anterior pituitary secretion has also not been investigated. Both these problems deserve careful study. But regardless of whether the pituitary or some other cause is responsible, it seems quite definite that some condition accompanying lactation has increased the secretion in these dogs, and when it is realized that this secretion is accompanied by the marked erosion to be presently discussed, it assumes greater significance.

5. Hollander, F.: Gastric Hypersecretion Following Parturition in a Dog, Proc. Soc. Exper. Biol. & Med. **27**:303, 1930.

6. Corner, G. W.: Hormonal Control of Lactation, Am. J. Physiol. **95**:43, 1930.

7. Cushing, H.: I. The Reaction to Posterior Pituitary Extract (Pituitrin) When Introduced into the Cerebral Ventricles, Proc. Nat. Acad. Sc. **17**:163, 1931.

The Marked Erosion of the Fistula and the Abdominal Wall.—The second striking point noted about the pouches was the marked erosion of the abdominal wall that occurred around the fistula during lactation. The secretion, as shown in the tests, was certainly not profuse, but the erosion was more extensive than is usually seen in actively secreting Pavlov pouches in which the response to a meal is from 5 to 8 cc. per hour. In these pouches it was from 0.3 to 1 cc. per hour. The two possible explanations that present themselves are that (1) the juice, though small in quantity, was of a greater digestive power than normal and (2) the tissues of the abdominal wall were less resistant to the digestive factors in the juice.

Unfortunately the quantities of the secretion were so small that adequate determinations of pepsin could not be made. But in the tests that were performed by the Mett method in the third dog, there did not appear to be an excessive amount of pepsin.

The second possibility, as before mentioned, is that there is a diminished resistance to the digestive juice. A consideration of this question involves, of course, a discussion of the resistance of living cells to ferments. A very extensive literature exists on this subject,[8] and it chiefly revolves about the question of antiferment. Whether or not in the foregoing experiments there existed a diminution of antiferments in the tissues of the abdominal wall cannot be stated at present.

However, whichever of these two factors may be the significant one, it seems quite definite that an imbalance existed, and the potency of a small amount of gastric juice in creating the severe digestive erosions was very striking. It may incidentally be recalled what marked variations exist in persons in the amount of erosion present around a gastric fistula.

The rôle of gastritis as a precursor of ulcer has recently been widely discussed (Konjetzny). Some observers think that acid and pepsin are important elements in the production of gastritis. In patients in whom it develops, some such imbalance may be responsible.

The observation, then, that increased secretion takes place in transplanted gastric pouches during lactation and that the resultant juice possesses a greater than normal digestive power toward the tissues of the abdominal wall of the same animal may be of clinical importance. Further lines of investigation of the subject are readily suggested, as indicated.

8. Some of the more important recent articles are: Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. 8:791 (May) 1924. Necheles, H.; Ling, J., and Fernando, F.: The Fate of Organs Transplanted into the Duodenum, Am. J. Physiol. 79:1, 1926. Necheles, H., and Fernando, F.: The Rôle of Trypsin and Anti-Trypsin, Am. J. Physiol. 79:9, 1925. de Takáts, G., and Mann, F. C.: The Effect on the Jejunal Mucosa of Transplantation to the Lesser Curvature of the Stomach, Ann. Surg. 85:698, 1927.

SUMMARY AND CONCLUSIONS

1. In gastric pouches transplanted to the subcutaneous tissues of the abdominal wall and completely separated from the old blood and nerve supply there was an increase of the quantity of secretion and of the concentration of hydrochloric acid during lactation. This was repeatedly observed.

2. When no secretion was present prior to lactation, it first appeared during that time.

3. In one case in which all the puppies died and there was no period of lactation, no increased secretion was observed.

4. Accompanying this increased secretion was a marked erosion of the abdominal wall around the opening of the pouch that was entirely out of proportion to the quantity of the secretion.

5. The possibility is discussed that the dilatation of the blood vessels in the abdominal wall during lactation is responsible for these phenomena by increasing the circulation. After a consideration of the factors, including experiments on diminishing the blood supply, the conclusion is reached that though a vascular supply may in part be responsible, other factors also play a rôle.

6. That these other factors are associated with the state of lactation itself is rendered probable, as the same phenomena were also observed when the original gastric blood supply was intact and when the blood supply of the abdominal wall was not concerned.

7. The causative factor for the increased secretion is at least partly humoral, since in one dog the transplanted pouch consisted only of mucous membrane and submucosa completely severed from the stomach. The vagus, the sympathetics, the gastric blood vessels and the myenteric plexus were eliminated.

GASTRIC SECRETION

IV. THE EFFECT OF ATROPINE ON THE SECRETION OF TRANSPLANTED GASTRIC POUCHES

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A perusal of the results obtained by the clinical and experimental use of atropine on gastric secretion is bewildering. In part, this is due to the facts that (1) different sorts of stimuli are used to induce secretion (various kinds of test meals, alcohol, histamine) and that these stimuli vary not only in quality but in quantity, (2) that the amounts of atropine used to inhibit the secretion vary and (3) that the atropine is administered in different ways, for instance, by mouth or subcutaneously. Nevertheless, the impression is gained that the foregoing variables alone do not account for the diversity of results.

The commonly accepted classification of gastric secretion is: (1) the primary or cephalic, (2) the secondary or gastric and (3) the intestinal.

The primary phase is reflex, and the impulse is transmitted to the stomach over the vagi following the seeing, smelling, tasting or chewing of food. Since atropine depresses the parasympathetic system, one would expect it to depress or inhibit completely this primary phase. That this is true in dogs was demonstrated by Uschakow.[1]

What atropine does to the secondary or gastric phase of secretion is, however, not so clear. This phase follows the entrance of food into the stomach and is due to chemical stimulation acting on the antrum or the distal portion of the stomach. . Either the chemical stimuli (secretogogues) are directly absorbed into the blood stream through the antrum, or a hormone is formed in the antrum and carried to the glands of the body and fundus.[2] The latter view is the more prevalent. The vagi also seem to be concerned in the mechanism of this phase (Orbeli[3]), for after their section the secretion is diminished.

From the Surgical Service of Dr. A. A. Berg and from the Laboratory of the Mount Sinai Hospital.

1. Uschakow: Diss., St. Petersburg, p. 20; quoted by Babkin, B. P.: Die äussere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1928, p. 398.

2. For a summary of the subject, see Ivy, A. C.: The Rôle of Hormones in Digestion, Physiol. Rev. **10**:282, 1930.

3. Orbeli, L. A.: De l'activité de glandes à pepsine avant et après la section des nerfs pneumogastriques, Arch. di sc. biol. **12**:71, 1906.

The third phase is the intestinal. It, too, is due to chemical stimuli, either directly absorbed into the blood stream or first causing a hormone to be formed. This phase is inhibited by atropine (Ivy, Lim and McCarthy [4]).

The experiments to be reported here are chiefly concerned with the effect of atropine on the secondary or chemical phase. As some of the studies were on dogs with Pavlov pouches, however, observations on the primary phases are also included.

METHODS

Three types of dogs were used:

1. Two dogs with the usual Pavlov pouches (fig. 1). These pouches are supplied by both vagus and sympathetic nerves and by the normal blood supply. They are supposed to mirror accurately the secretory conditions in the whole stomach.
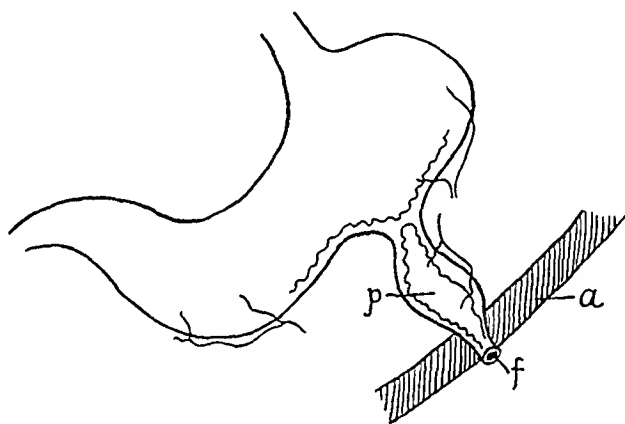
Fig. 1.—Pavlov pouch. Blood vessels and nerves intact. Only mucous membrane divides pouch lumen from stomach. The pouch is indicated by *p;* the abdominal wall by *a,* and fistula of pouch by *f.*

2. A dog with a Haidenhain pouch (fig. 2). This type of pouch is entirely separated from the stomach and is believed to have no vagus innervation. It is possible that sympathetic nerves still reach it along the blood vessels.

3. Four dogs with transplanted subcutaneous gastric pouches (fig. 3) prepared only from the mucous membrane and submucosa of the body and fundus (Klein [5]). In these pouches the vagi, the sympathetics and the myenteric (Auerbach's) plexus are eliminated. They are dependent for their blood supply on the abdominal wall and have no other communication with the gastric blood supply. In one of the dogs of this group, however, the original blood supply was left intact.

4. Ivy, A. C.; Lim, R. K. S., and McCarthy, J. B.: The Intestinal Phase of Gastric Secretion, Quart. J. Exper. Physiol. **15**:55, 1925.

5. Klein, E.: Gastric Secretion: II. A Transplanted Subcutaneous Gastric Pouch Without Auerbach's Plexus, Arch. Surg. **25**:442 (Sept.) 1932.

In the first type of dog both primary or vagal and secondary or humoral phases of secretion were present. In the third type, only humoral secretory stimuli reached the pouch, and atropine was therefore necessarily limited in its effect on stimuli carried through the blood stream. The possible sites for its action were further narrowed by the removal of the myenteric plexus.

In the majority of tests 1 mg. of atropine was injected subcutaneously. This dose was used because it gave definite evidences of physiologic effect and was never toxic. Keeton, Luckhardt and Koch[6] had reported that they could con-
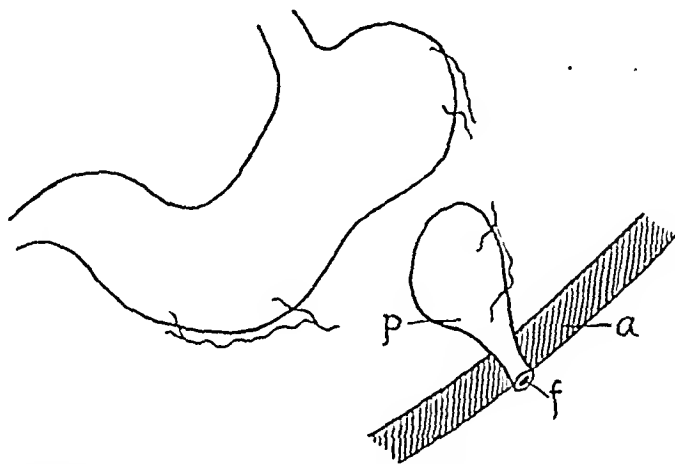
Fig. 2.—Haidenhain pouch. Vagi severed. Some sympathetic nerves enter with blood vessels, which are left intact.
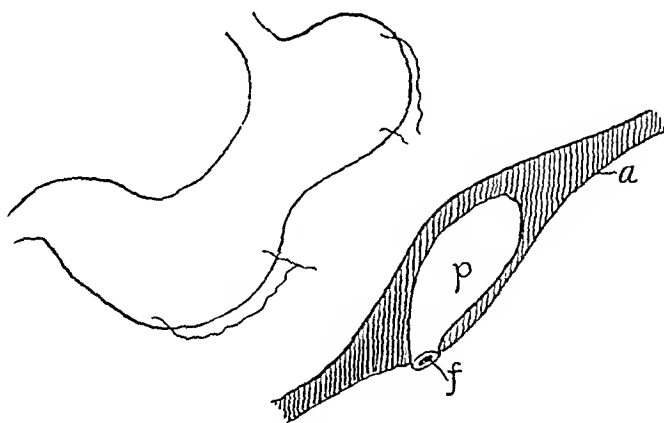
Fig. 3.—Transplanted subcutaneous pouch. Gastric blood vessels, vagi and sympathetic nerves completely severed. Myenteric plexus removed. Pouch walls consist of mucous membrane and submucosa.

stantly produce an anacidity in dogs with the same dose. They used it intramuscularly. The dogs all weighed from 10 to 12 Kg. The injection was usually given after an hour of control observation and was then followed fifteen minutes later

6. Keeton, R. W.; Luckhardt, A. B., and Koch, F. C.: Gastrin Studies: Response of the Stomach Mucosa to Food and Gastrin Bodies as Influenced by Atrophine, Am. J. Physiol. 51:469, 1920.

by a meal of 250 Gm. of meat and 250 cc. of water. Occasionally the atropine was given at the time of the meal or earlier. Secretion was collected from the pouches every hour. Free acid was tested by Toepfer solution against tenth-normal sodium hydroxide and total acid by phenolphthalein. When sufficient secretion was present, determinations of pepsin and total chloride were often made. Pepsin was determined by Mett tubes after diluting the secretion sixteen times with twentieth-normal hydrochloric acid and incubating for twenty-four hours. The results are expressed as units of pepsin determined by squaring the millimeters of pepsin

TABLE 1.—*Action of Atropine on Pavlov, Haidenhain and Transplanted Gastric Pouches Without a Myenteric Plexus. One Milligram Was Injected Sub-cutaneously Fifteen Minutes Before a Meal of 250 Gm. of Meat and 250 Cc. of Water. Control Tests Are Made Without Atropine*

Hour	Volume of Juice, Cc.		Free Hydrochloric Acid		Total Hydrochloric Acid	
	Without Atropine	After Atropine	Without Atropine	After Atropine	Without Atropine	After Atropine
Dog M., with Pavlov Pouch						
1................	0.6	0.9	56	26	92	40
Fed meat and water						
2................	11.0	0.2	78	0	120	0
3................	13.5	0	38	—	82	—
4........	10.2	0	40	—	86	—
5................	9.0	0.4	36	18	74	30
6................	7.2	0.8	46	16	96	36
Dog N., with Haidenhain Pouch, 1.5 Mg. Atropine Used						
Fed meat and water						
1................	1.2	0.2	78	0	96	+
2..	1.4	0.5	86	0	102	6
3........	2.8	0.7	72	0	94	8
4......	4.6	1.2	80	Trace	86	6
5................	3.5	2.0	88	8	104	10
Dog A., with Transplanted Gastric Pouch without Myenteric Plexus						
1................	...	1.8	..	0	..	35
Fed meat and water						
2................	2.2	2.7	55	0	75	35
3................	3.5	2.8	70	0	95	30
4................	3.8	1.6	75	0	100	35
5................	5.5	1.4	70	0	95	40
6................	2.5	0.6	85	0	110	30
Dog C., with Transplanted Gastric Pouch without Myenteric Plexus						
1................	0.1	0	—	—	—	—
Fed meat and water						
2................	1.3	0	75	—	120	—
3................	0.8	0	60	—	115	—
4................	1.2	0	50	—	100	—
5................	0.9	0	55	—	115	—
6................	0.6	0	70	—	125	—

digested and multiplying by sixteen. The total chlorides are expressed as cubic centimeters of tenth-normal solution to make them easily comparable with the free and total acid.

RESULTS

1. Atropine in doses of from 1 to 1.5 mg. given in the manner outlined can suppress the secretion of free hydrochloric acid in Pavlov, Haidenhain and transplanted subcutaneous gastric pouches (table 1). This indicates that in these tests atropine abolished the secretion. It is interesting to note that the second or Haidenhain pouch was the only one that never became anacid after the administration of 1 mg. of atropine;

1.5 mg. was necessary. Whether this was due to an imbalance created by the absence of the vagi and presence of sympathetics can only be conjectured.

2. In the dog with the latter type of pouch, 1.5 mg. of atropine given five minutes after a meal produced merely a decreased secretion. When

TABLE 2.—*Action of Atropine on Dog N., with Haidenhain Pouch Before and After Meal of 250 Gm. of Meat and 250 Cc. of Water*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid
1.5 Mg. Atropine Injected Five Minutes after Meal			
1	1.7	10	14
2	2.6	12	14
3	3.5	12	14
4	2.3	10	12
5	2.0	8	10
1.5 Mg. Atropine Injected Five Minutes before Meal			
1	0	—	—
2	0	—	—
3	0.2	0	÷
4	0.2	0	±
5	0.8	0	10

TABLE 3.—*Effect of Injecting 1 Mg. of Atropine Fifteen Minutes After 1 Cc. of Histamine, Showing That Atropine Does Not Abolish the Histamine Secretion*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid
Dog A., with Transplanted Gastric Pouch without Myenteric Plexus			
1	0.2	0	45
1 mg. atropine injected subcutaneously 15 minutes after histamine			
2 hr. 15 min.	2.7	40	70
3 hr. 15 min.	0.4	0	45
4 hr. 15 min.	0.65	0	35
5 hr. 15 min.	0.8	0	35
6 hr. 15 min.	0.5	0	25
Dog Cac., with Transplanted Gastric Pouch without Myenteric Plexus			
1	1 drop	0	—
1 Mg. atropine injected subcutaneously 15 minutes after histamine			
2 hr. 15 min.	5.2	100	120
3 hr. 15 min.	0.4	45	60
4 hr. 15 min.	0	—	—
5 hr. 15 min.	0	—	—
6 hr. 15 min.	0	—	—

given thirty minutes before the meal, anacidity resulted (table 2). In the latter case, an atropinized animal to which the secretory stimulus was applied was being dealt with. In the former, the primary phase of secretion had already been stimulated, and perhaps some of the food in the stomach had initiated the secondary phase. Rall,[7] one of the few observers who reported anacidity after the administration of atropine

7. Rall, T.: Ueber den Einfluss des Atropins auf die sekretorische und motorische Funktion des gesunden Magens, Ztschr. f. d. ges. exper. Med. **52**:752, 1926.

TABLE 4.—*Effect of Injection of 1 Mg. of Atropine Fifteen Minutes Before Ingestion of 250 Gm. of Meat and 260 Cc. of Water, Showing That When Secretion of Hydrochloric Acid Was Present During the Control Hour Atropine Did Not Abolish Secretion, and When It Was Absent the Atropine Did Abolish the Secretion*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid	Pepsin	Total Chlorides
		Dog E., with Pavlov Pouch			
1..................	1.2	50	85	...	...
Fed meat and water fifteen minutes after atropine subcutaneously					
2..	2.8	55	70	400	156
3.....	2.5	95	105	144	156
4....	2.3	80	95	...	140
5.....	2.5	90	100	672	154
6..................	3.1	80	95	576	150
	Experiment Repeated on Same Dog When No Secretion Was Present in the First Hour				
1..................	0.2	0	—	..	...
Fed meat and water fifteen minutes after atropine subcutaneously					
2..................	0.3	0	45	..	..
3..................	0.5	0	50	...	.
4......	1.0	30	85	. .	...
5..................	2.0	75	95	144	150
6..................	1.8	80	110	256	160
	Dog Cae., with Transplanted Gastric Pouch without Myenteric Plexus				
1..................	4.9	45	80	16	148
Fed meat and water fifteen minutes after atropine subcutaneously					
2..................	3.1	50	70	16	144
3.....	9.6	40	75	9	142
4..................	1.0	25	60	...	. .
5.................	1 drop	—	—	. .	...
6..................	0	—	—	...	...
	Experiment Repeated on Same Dog When No Secretion Was Present in the First Hour				
1..................	0	—	—	...	...
Fed meat and water fifteen minutes after atropine subcutaneously					
2..................	0	—	—	..	.
3..................	0	—	—	...	...
4..................	0.3	35	60	..	.
5..............	0.4	25	55	.	...
6..................	0.4	30	65	...	...

TABLE 5.—*Effect of Injection of 1 Mg. of Atropine on Spontaneous Secretion in Dog Cae., Having Transplanted Gastric Pouch Without Myenteric Plexus*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Hydrochloric Acid
1..	1.4	110	120
1 mg. atropine injected subcutaneously			
2..	1.6	72	80
3..	0.6	30	60
4..	2.7	50	70
5..	1.1	20	52
6..	0	—	—

in man, noticed the same fact. He used bouillon as a test meal. One milligram of atropine, one hour before the meal, produced anacidity. At the time of the meal it was ineffectual. The possible cause will be discussed later.

3. If 1 cc. of histamine was administered fifteen minutes after 1 mg. of atropine, the response to histamine was almost the same as without the atropine. Occasionally it was slightly reduced. This was true of all the types of pouches (table 3). It had previously been observed by Keeton, Luckhardt and Koch[6] in Pavlov pouches. It is evidently true of the Haidenhain pouch and of the transplanted pouch without the myenteric plexus.

4. Two dogs showed another interesting phenomenon. One of these was of the first group (with a Pavlov pouch) and one of the last group. In the latter a pouch, consisting only of mucous membrane and submucosa, had been transplanted as in the others, but the original blood supply was left intact. At times 1 mg. of atropine inhibited the secretion; at other times it did not. Examples are shown in table 4. Analysis of these results showed that when secretion was present during the control hour the atropine was ineffectual. When no secretion was present, the atropine inhibited the stimulus of food. This was repeatedly observed. In the dog with the transplanted pouch it was also found that spontaneous secretion such as noted in the control hour frequently occurred. This has previously been reported in this type of pouch (Klein[5]). Atropine lowered but did not abolish this spontaneous secretion (table 5). There is evident here a stimulus that is apparently humoral and which, like histamine and gastrin, is not completely suppressed by atropine.

<div align="center">COMMENT</div>

In the foregoing experiments two observations should be emphasized:
1. Following a meal of meat and broth atropine can abolish the secretion of free hydrochloric acid in a Haidenhain pouch and in transplanted pouches. The latter were without vagus or splanchnic innervation and without the myenteric plexus. This would tend to show that in dogs atropine can abolish the humoral secretion of the secondary or gastric phase. Stimuli from the stomach could reach the latter pouches only through the blood stream.

2. In two dogs when secretion of free hydrochloric acid was present before the tests began the atropine was ineffectual. This was noted in a dog with a Pavlov pouch, but was especially marked in a dog with a transplanted pouch. In the case of the dog with a Pavlov pouch it is possible that the spontaneous secretion may have been vagal and similar to the fasting secretion in man. If so, it is likely that the atropine would have inhibited it. In the dog with the transplanted pouch, however, this

secretion was necessarily humoral and not reflex in nature. Like the secretion of histamine, it could not be abolished by atropine in doses of 1 mg.

The origin of this secretion is obscure, but it must have come either from the gastro-intestinal tract or from the parenteral tissues. As the dog had not been fed for twenty-four hours, stimulation by food from the stomach and small intestine seems excluded. Food substances introduced into the large intestine through the rectum do not stimulate gastric secretion. Saliva, bile and pancreatic juice in the stomach are known to stimulate the second phase. However, it would seem that since the other intragastric stimuli (water, meat) were rendered ineffectual by atropine, these also may have been inhibited. There is left the interesting possibility that the humoral stimulant was of parenteral origin. Such parenteral stimuli have previously been assumed by Bickel[8] and Krimberg.[9] In view of the fact that atropine did not abolish this stimulus, it probably acts like histamine directly on the cell.

On the other hand, atropine did completely inhibit the action of the humoral stimuli which originated from food inside the stomach, that is, from the test meal. This observation was previously made in a different way by Zeliony and Sawitsch[10] and by Sanozky.[11] The former found, for instance, that the secretion due to beef extract placed in an antral pouch could be inhibited by atropine. But if the beef extract were injected subcutaneously or intravenously, atropine could not prevent the secretion.

The question naturally arises as to why the atropine inhibits the humoral stimulus produced by food but does not inhibit the humoral secretion of parenteral origin. Two possible answers to this question are: 1. The secretory hormone produced by food in the antrum and intestine may differ chemically from the other humoral stimulant, and also from other substances, such as beef extract, histamine and gastrin, which, after subcutaneous injection, cause secretion; further, the latter may act directly on the secretory cell, while the hormone may act on nerve endings that are paralyzed by atropine, or (2) atropine prevents the formation of the gastric hormone in dogs. The first possibility cannot be answered until more is known of the hormone. The second possibility will be discussed.

8. Bickel, A.: Der nervöse Mechanismus der Sekretion der Magendrüsen und der Muskelbewegung am Magendarmkanal, Ergebn. d. Physiol. 24:228, 1925.

9. Krimberg, R.: Zur Frage nach der Bedeutung der Muskelhormone im Sekretionsprozesse der Verdauungsdrüsen, Biochem. Ztschr. 157:187, 1925.

10. Zeliony and Sawitsch: Verhandl. d. ges. russ. Aerzte zu St. Petersburg, 1912; quoted by Babkin (footnote 1, p. 399).

11. Sanozky: Diss., St. Petersburg, 1893, p. 80; quoted by Babkin (footnote 1, p. 398).

The Site of Action of Atropine.—The site of action of atropine is usually considered to be on the postganglionic nerve endings in the cells or neurocellular substance, but the subject is not clearly settled. There is some evidence, for instance, that in large doses it may act directly on the gastric secretory cells (Keeton, Luckhardt and Koch[6]). In the case of the motor cells the chief action also seems to be on the nerve endings or neuromuscular junction. But here it has more definitely been shown (Cushny[12]) that atropine may also act directly on the cell.

The foregoing experiments definitely show that complete inhibition of secretion may be produced by atropine in the absence of the myenteric plexus. More precise conclusions as to the site of action could be drawn from these experiments if one were certain of the nature of the submucous (Meissner's) plexus. If the latter were definitely sympathetic, then the postganglionic vagus fibers to the secreting cells would originate in the myenteric plexus. Since this plexus had been removed and since the sympathetics were also eliminated, the secreting cells of the transplanted pouch would then be left without any efferent nerve endings. Both autonomic systems would be eliminated. But although there does exist evidence that the submucous plexus is sympathetic and although in a previous paper I subscribed to this view, I am at present uncertain as to this. The possibility therefore still exists that atropine could act on nerve endings in the pouches mentioned. This subject will be more fully discussed in a subsequent paper on the action of pilocarpine.

One other possible site of action deserves further mention. Ivy[2] advanced the suggestion that atropine may prevent the formation of the hormone in the stomach. There is no parallel action of such a nature known, but, as already stated, this hypothesis would explain the experiments of Zeliony and Sawitsch.[10] If beef extract was placed in the antrum of the stomach, atropine inhibited the secretion, but after subcutaneous injections atropine was ineffectual. This hypothesis would also explain the observation mentioned that the same dose of atropine which before a meal inhibited secretion was ineffectual if given after the onset of the meal. It is possible that when given before the meal it prevented the formation of hormones, and that after the latter had been formed and were already present in the blood the atropine was ineffectual.

In the dog, then, atropine can abolish all three phases of secretion. Uschakow[1] showed that it could abolish the first phase. Sanozky and Zeliony and Sawitsch showed that it abolished the secretion due to chemical stimuli in the stomach, and I have now shown the same result in transplanted pouches deprived of all peripheral nerve supply and

12. Cushny, A. R.: Handbuch der experimentellen Pharmakologie, translated into German by A. Heffter, Berlin, Julius Springer, 1920, vol. 2, pt. 2, p. 631.

subject only to humoral influences. Ivy, Lim and McCarthy [4] reported that it abolishes the intestinal phase.

Action of Atropine on Man.—In man, however, the reports on the action of atropine vary considerably. On the one extreme are results such as those of Crohn,[13] who found an increase, and on the other, results of Rall,[7] who found complete abolition. The majority of observers report only a reduction in acidity which varies in different groups of subjects (Keefer and Bloomfield,[14] Schiff,[15] Bennett,[16] Lockwood and Chamberlin,[17] Kellerman [18]).

It cannot be said conclusively that atropine always abolishes the primary or reflex phase in man, but there are some suggestive facts. Thus Winkelstein [19] reported that after partial gastrectomy and removal of the second phase atropine probably suppresses the primary or reflex phase.

The chemical phase cannot, however, be suppressed. Pokras and Michelson [20] attempted to produce a condition in which the primary phase was eliminated by feeding the patients through a stomach tube. In ten of fifteen cases the resultant secretion could be diminished in varying degrees. Kliutschareff [21] from similar studies came to the conclusion that in cases of gastric hyperacidity a definite drop with atropine can be obtained only if a large part of this hypersecretion is due to the first phase. Hypersecretion is, of course, not normal.

The reason for this difference of action in the second phase between man and dog is unknown. It is possible, however, that in man more of the humoral stimuli act directly on the cell. Under these conditions atropine would be relatively less effectual.

Hypersecretion is usually considered to be of nerve origin. Should a condition such as humoral hypersecretion be established, its origin and

13. Crohn, B. B.: Am. J. M. Sc. **155**:801, 1918.

14. Keefer, C. S., and Bloomfield, A. L.: The Effect of Atropine on Gastric Function in Man, Arch. Int. Med. **38**:303 (Sept.) 1926.

15. Schiff, Arthur: Beiträge zur Physiologie und Pathologie der Pepsinsecretion, Arch. f. Verdauungskr. **6**:107, 1900.

16. Bennett, T. I.: The Modification of Gastric Function by Means of Drugs, Brit. M. J. **1**:366 (March 3) 1923.

17. Lockwood, B. C., and Chamberlin, H. G.: The Effect of Atropin on Gastric Function, as Measured by Fractional Analysis, Arch. Int. Med. **30**:806 (Dec.) 1922.

18. Kellerman, Emil: Untersuchungen mit der fraktionierten Magenausheberung, Arch. f. Verdauungskr. **45**:67, 1925.

19. Winkelstein, Asher: Gastric Secretion After Partial Gastrectomy for Ulcer, Am. J. Surg. **7**:494, 1929.

20. Pokras, S., and Michelson, V.: Vegetatives Nervensystem und Magensekretion, Arch. f. Verdauungskr. **38**:373, 1926.

21. Kliutschareff, quoted by Pokras and Michelson (footnote 20).

nature would be of significance. For instance, the production of gastric anacidity after partial gastrectomy (which removes the antrum and therefore the chemical phase) would depend in part on the proportion of stimulating influences arising from the antrum. Perhaps in these relations lies a partial explanation of the observation mentioned in a previous paper;[22] namely, that partial gastrectomy for gastric ulcer is usually followed by anacidity, whereas after duodenal ulcer only 25 per cent become anacid.

SUMMARY

1. In the dog atropine in nontoxic doses (1 to 1.5 mg.) can abolish the secretion of hydrochloric acid produced by food in the Pavlov pouch, in the Haidenhain pouch and in transplanted subcutaneous gastric pouches without the myenteric plexus.

2. In the latter type of pouch the parasympathetic (vagi) and the preganglionic and postganglionic sympathetic nerves are eliminated. Whether the postganglionic parasympathetic nerves are also absent cannot be stated until the relations of the submucous plexus are definitely known.

3. At any rate, following food, only stimuli through the blood could reach this pouch. These stimuli could be completely eliminated by 1 mg. of atropine.

4. The method by which the humoral secretion from food is inhibited by atropine in the transplanted pouches is not clear. This action may take place either in the antrum or peripherally at the cells.

5. One milligram of atropine does not abolish the secretion of 1 cc. of histamine in these pouches. The histamine probably acts directly on the cell.

6. The same dose of atropine that could abolish stimulation by food when given fifteen minutes before a meal was ineffectual when given after a meal. This fact may be of use clinically.

7. In one dog with a transplanted pouch a spontaneous secretion was present at irregular intervals not associated with the test meal. This secretion was diminished by 1 mg. of atropine, but was not abolished. When it was present and a test meal was given, the atropine did not abolish the secretion. This spontaneous secretion could not have been due to vagus stimulation. It is possible that it was of parenteral origin and that its action was directly on the cell.

8. In man atropine apparently does not abolish the chemical phase of secretion. The differences and possible causes are briefly discussed.

22. Klein, E.: Gastric Secretion After Partial Gastrectomy, J. A. M. A. **89:** 1235 (Oct. 8) 1927.

9. It is possible that variations in the proportionate amount of the primary (cephalic) and secondary (chemical) phases of secretion partly account for (1) the lower acidity in gastric ulcers as compared to duodenal and (2) the far higher percentage of anacidity following partial gastrectomy for gastric ulcer. If in gastric ulcer a larger proportion of the secretion is due to the chemical phase from the antrum, the removal of this part of the stomach would account for the greater frequency of the anacidity.

ETIOLOGY OF GALLSTONES

III. EFFECT OF DIET ON THE BILE SALT-CHOLESTEROL RATIO

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It has been shown by us in previous papers [1] that the actual cholesterol content in the bile is not so important in gallstone formation as the ratio of the cholesterol to the substance that holds it in solution, that is, the bile salts. Therefore, it becomes important to study the factors influencing this ratio. The single factor of the concentration of the cholesterol and of the bile salts taken separately have each received much previous attention, and there is a large literature on the subject which it is not necessary to review here. However, the important factor of simultaneous estimation of the two substances has rarely been employed, and the following studies are an attempt to fill this gap. This paper will be mostly concerned with the cholesterol factor in this ratio and with attempts to vary bile cholesterol by the administration of fat or lipoids. The literature on the biliary excretion of cholesterol is rather extensive, and the results reported are apparently so contradictory that before presenting our own data, a critical review is necessary.

The earliest work of importance on this subject was done in Naunyn's laboratory in Strasbourg in the early nineties. Naunyn believed that gallstones originated in the secretion of the mucosa of the gallbladder, and the following three sets of experiments were done under his direction. Jankau [2] used both dogs and rabbits in his experiments, making biliary fistulas and estimating the cholesterol content of the fistula bile under various conditions of feeding. He found that the administration of enormous amounts of cholesterol in oil (5.5 Gm.),

1. Andrews, E.; Schoenheimer, R., and Hrdina, L.: Etiology of Gallstones: I. Chemical Factors and the Rôle of the Gallbladder, Arch. Surg. **25**:796 (Oct.) 1932. Andrews, E.; Hrdina, L., and Dostal, L. E.: Etiology of Gallstones: II. Analysis of Duct Bile from Diseased Livers, Arch. Surg. **25**:1081 (Dec.) 1932.

2. Jankau, L.: Ueber Cholesterin und Kalkausscheidung mit der Galle, Arch. f. exper. Path. u. Pharmakol. **19**:237, 1891.

either subcutaneously or by mouth, caused no rise in the biliary choles-
terol. Examination of the intestine or the area of injection showed that
the cholesterol had disappeared. Intraduodenal injections led to similar
results. Thomas,[3] also using both dogs and rabbits with biliary fistulas,
studied the effect of diets of meat, bread or fat, and likewise found no
changes in the biliary cholesterol in a considerable series. Kauseh[4]
performed feeding experiments with negative results, and also analyzed
the bile from cadavers in many diseases and found no significant increase
in any. These experiments led Naunyn[5] to conclude that the cholesterol
content of bile was independent of any alimentary influences, and not
related to the blood cholesterol or any disease process.

The work cited has been questioned on several grounds. In the
first place it was done before any modern chemical methods for accurate
cholesterol estimation were devised. This is undoubtedly true and,
furthermore, the figures given are in many cases quite outside the range
that later observers with better methods have found in similar fluids.
It must be admitted, however, that considering the methods available
the work seems remarkably accurate, and while the absolute values may
not be correct, the lack of change in the relative values cannot be so
lightly dismissed.

Little work was done on the subject for about twenty-five years;
then the introduction of the Lieberman-Burchard colorimetric method
of estimation of cholesterol in small amounts of blood gave rise to
many further investigations. Naunyn's views of gallstones as resulting
from catarrh of the gallbladder were discarded, and the exact opposite,
the theory of "cholesterol diathesis," supplanted them. It was reasoned
that a high blood cholesterol implied a high bile cholesterol, and gall-
stones were thus easily explained. An enormous volume of papers were
published on this subject for the next ten years. These need not be
enumerated here; it is sufficient to say that the more careful workers
found no evidence of raised blood cholesterol with gallstones in the
absence of biliary obstruction. One of us (E. A.) made 250 such
estimations in 1916-1917, and was quite disappointed to find no corre-
lation whatsoever. It was not until 1924, however, that the elaborate
and careful studies of Campbell[6] finally and conclusively laid the ghost
of this theory by showing that the average patient with gallstones had a

3. Thomas: Ueber Abhängigkeit der Absonderung und Zusammensetzung der
Galle von der Nährung, Dissert., Strasbourg, 1890.

4. Kausch: Ueber den Gehalt der Leber an Galle und Cholesterin, Dissert.,
Strasbourg, 1891.

5. Naunyn, B.: A Treatise on Cholelithiasis, London, New Sydenham Society,
1896.

6. Campbell, J. M. H.: Cholesterol in Blood in Cases of Gall-Stones. Quart. J.
Med. **18**:123, 1924.

normal amount of blood cholesterol. Not only Campbell's own work but his careful review of the subject is important.

In the meantime sporadic papers had appeared on the relation of blood cholesterol to bile cholesterol. In 1907 Goodman [7] showed that the destruction of erythrocytes in vivo raised the cholesterol of the blood, and Kusumoto's [8] careful work on the bile in animals poisoned with tolylenediamine (a strongly hemolytic agent) showed a large increase in the cholesterol excreted in the bile. This work is not open to criticism from a chemical standpoint, but the interpretation put on it by other workers is, in our opinion, totally unwarranted. The blood cholesterol in ordinary normal or pathologic persons is certainly not to be compared to that loosed by disintegration of red cells by poisons. While a part of our blood cholesterol may, without doubt, have such an origin, it certainly is but a small part, as this would imply a much faster normal replacement than actually takes place. Such experiments are surely not to be taken as proof that a high blood cholesterol implies a high bile cholesterol in general.

Bacmeister [9] studied the bile in diabetic patients with fistulas, and concluded that the cholesterol averaged higher than in normal persons. The differences he found were, however, not far outside the normal limits when the marked variability of biliary cholesterol is taken into consideration. This work has been cited by McNee as evidence of a relation of bile and blood cholesterol, although Bacmeister himself concluded that his results were secured "nicht allein durch die verschiedene Nährungsform erklären lassen [not only through the different forms of diet explained]." In two diabetic patients coming under our observation the cholesterol in fistula bile was within normal limits. In one of these a twenty-four hour sample was possible, and it also was normal. (Experimental studies on this subject are being undertaken.)

Peirce [10] studied the type of cholesterol in a series of human biles. He found that esters were very low and that free cholesterol made up the majority. While his work has been quoted as showing a relation between blood and bile cholesterol (e. g., in nephritic patients it was high), careful examination of his tables shows that cholesterol was even higher in other conditions not associated with hypercholesteremia.

7. Goodman, E. H.: Ueber den Einfluss der Nährung auf die Ausscheidung von Gallensäuren und Cholesterin durch die Galle, Beitr. z. chem. Physiol. u. Path. 9:91, 1907.

8. Kusumoto, C.: Ueber den Einfluss des Toluylendiamins auf die Ausscheidung des Cholesterins in der Galle, Biochem. Ztschr. 13:354, 1908.

9. Bacmeister: Untersuchungen über Cholesterinausscheidung in menschlichen Gallen, Biochem. Ztschr. 26:223, 1910.

10. Peirce, S. J. S.: Der Gehalt der menschlichen Galle in Cholesterin und Cholesterinestern, Deutsches Arch. f. klin. Med. 106:337, 1912.

Havers'[11] experiments on dogs revealed a slight increase in the biliary cholesterol after the feeding of fat. It became less in febrile conditions and, most interesting of all, it appeared to be definitely decreased in pregnancy. The latter fact led Havers to the hypothesis that the well known hypercholesteremia of pregnancy is a retention due to the fact that not enough is excreted in the bile. Such a concept of hypercholesteremia, while it has but little evidence in its support as yet, must be kept in mind as a possibility in many other conditions besides the classic example of jaundice.

D'Amato[12] showed that the cholesterol in the bile was diminished markedly in intoxication by liver irritants. The injection of alcohol, amyl alcohol, acetic acid or butyric acid had this effect. The subcutaneous injection of Bacillus coli had a similar effect. As will be seen later, the authors have shown that ether may have a similar action, although the effect is variable.

One of the most important observations was that of Rothschild[13] in 1915. He showed that the amount of cholesterol in the blood, in the liver and, most significantly, in the bile was enormously increased by starvation. While the now well known fact of starvation lipemia is not of interest here, it would be important to get evidence of gallstone formation in such cases. Evidence for or against this to our knowledge is almost totally lacking in spite of the widespread condition during the war and postwar periods. Rothschild's observations have been confirmed by McMaster[14] and others. The interesting point is that from the standpoint of degree such changes tend to mask all others, as they are so extremely great. The biliary cholesterol may be more than tripled in a short time by starvation, and this is the only method ever reported which had led to anything approaching such concentrations. Whether the concomitant desiccation of the body with consequent concentration of the bile is adequate to explain it is doubtful. The well known starvation syndrome of edema resembling lipoid nephrosis may give rise to a much greater endogenous production of cholesterol by the breaking up of body cells and the accumulation of insoluble and slowly excreted cholesterol. In our experiments on dogs this has

11. Havers, K.: Experimentelle Untersuchungen über Physiologie und Pathologie des Cholesterinstoffwechsels mit besonderer Berücksichtigung der Schwangerschaft, Deutsches Arch. f. klin. Med. **115**:267, 1914.

12. D'Amato, L.: Chemische Veränderungen der Galle bei Leberintoxikationen und ihre Wichtigkeit in der Pathogenese der Gallensteinkrankheit, Biochem. Ztschr. **69**:353, 1915.

13. Rothschild, M. A.: Zur Physiologie des Cholesterinstoffwechsels: V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand, Beitr. z. path. Anat. u. z. allg. Path. **60**:227, 1915.

14. McMaster, P. D.: Studies on Total Bile, J. Exper. Med. **40**:25, 1924.

often served to mask other, smaller changes, and it is to be constantly kept in mind in any studies on this subject, as it has been a fertile source of error.

McNee[15] studied the gallbladder bile in pregnant women dying of septic abortion and found its cholesterol content higher than normal. From this he concluded that the hypercholesteremia of pregnancy was accompanied by an increase in the bile cholesterol.[16] This conclusion is open to grave question. In the first place, the agonal changes in the liver and the obvious antemortem starvation in such cases make it rather doubtful if postmortem material of this type can apply to the normal pregnant woman. Again, there is a tendency, which we have noted previously,[15] for the gallbladder to concentrate dilute biles to somewhat the same concentration as normal biles. The concentrating process tends to continue until the total solids reach the level of about 25 per cent. This view of McNee's has received more widespread notice in his summary of the knowledge of cholesterol metabolism, and again in Rolleston and McNee's "Diseases of the Liver, Gall Bladder and Bile Ducts."[18]

Further support was given to these theories by Stepp,[19] who reported a slight decrease (from 10 to 15 per cent) in the bile cholesterol in animals on a lipoid-free diet. This seems a rather small change on which to base any conclusions in a field in which the normal, uncontrolled variations are ten times as great. Pribrams'[20] studies on the bile of pregnant women yielded much more striking results. He found that during the first months of pregnancy the cholesterol content of the bile was low but later reached excessively high figures which persisted for a considerable period after delivery. His figures showed a degree of change far beyond the possibility of experimental error. However, his specimens were derived by duodenal intubation, and the liver bile and gallbladder bile were fractioned according to the Meltzer-Lyon technic. He believed that he was correct in stating that not one clinician in ten today has any confidence that specimens obtained in this manner can be definitely assigned any origin. Secondly, as will be shown, most of the

15. McNee, J. W.: Zur Frage des Cholesteringehalts der Galle während der Schwangerschaft, Deutsche med. Wchnschr. **39**:994, 1913.

16. McNee, J. W.: Cholesterin, an Account of Its Relations to Pathology and Physiology, Quart. J. Med. **7**:221, 1914.

17. Andrews, Schoenheimer and Hrdina (footnote 1, first reference).

18. Rolleston, R., and McNee, J. W.: Diseases of the Liver, Gall Bladder and Bile Ducts, ed. 3, London, The Macmillan Company, 1920.

19. Stepp, W.: Beobachtungen über den Cholesteringehalt des Blutes und der Galle bei Lipoidfrei ernährten Thieren, Ztschr. f. Biol. **69**:514, 1919.

20. Pribram, E. C.: Zur Frage des Cholesterinstoffwechsels während der Schwangerschaft und im Wochenbett, Arch. f. Gynäk. **120**:90, 1923.

intestinal sterols are not biliary in origin. These two facts, to our mind, completely vitiate the results of this work.

The most recent study on this subject has been the reports of a series of English investigators, whose results substantiate the theory that ingested cholesterol does not appear in the bile. Fox,[21] in a carefully controlled series of studies, was not able to demonstrate the slightest effect of diet. Gardner and Gainsborough,[22] in their masterly review of cholesterol. metabolism, stated that they did not believe that biliary cholesterol can be affected by diet. Gainsborough,[23] in a study of so-called lipoid nephrosis in which the blood cholesterol reached very high levels, found normal amounts in the bile.

Finally come the elaborate studies of Peyton Rous and his associates, which were reviewed by us in a previous paper. These studies were done in the only really scientific manner, as they used the two-way fistula of McMaster,[24] so that the bile after sampling was returned to the intestine. Their results showed a slight rise from diets rich in cholesterol, but an increase in the cholesterol of the bile from starvation which overshadowed all other influences.

To show the absurdity of much of the previous work on the subject, it is only necessary to call attention to the fact that it was done utilizing complete biliary fistulas from either the clinic or the experimental laboratory. It has repeatedly been shown in such cases that all fatty material passes through the gastro-intestinal tract unchanged under such circumstances and can be recovered quantitatively in the stools. The evidence on this subject was summed up by Gardner and Gainsborough.[22] The futility of feeding experiments under such conditions is obvious. Added to this, it is interesting to note the crucial experiments of Schoenheimer,[25] showing that plant sterols are not absorbed at all.

It is a common misapprehension that most of the fecal sterols are biliary in origin. Since the early experiments of Voit[26] in 1892 it has been known that the mucosa of the gastro-intestinal tract secretes much lipoid material. This is not lessened, but on the contrary markedly

21. Fox, F. W.: The Composition of Human Bile and Its Bearing upon Sterol Metabolism, Quart. J. Med. **21**:107, 1927.

22. Gardner, J. A., and Gainsborough, H.: Blood Cholesterol Studies in Biliary and Hepatic Diseases, Quart. J. Med. **23**:465, 1930.

23. Gainsborough, H.: A Study of So-Called Lipoid Nephrosis, Quart. J. Med. **23**:101, 1929.

24. McMaster, P. D., and Elman, R.: Studies on Urobilin Physiology and Pathology: II. Relation of Bile to the Presence of Urobilin in the Body, J. Exper. Med. **41**:513, 1929.

25. Schoenheimer, R.: Ueber die Bedeutung der Pflanzensterine für der tierischen Organismus, Ztschr. f. physiol. Chem. **180**:1, 1929.

26. Voit, F.: Beiträge zur Frage der Secretion und Resorption im Dünndarm. Ztschr. f. Biol. **11**:325, 1892.

increased, if the bile is side-tracked by a biliary fistula. In the classic experiments of Sperry[27] on sterol absorption he found that from one and a half to four and a half times as much sterol was present in dog's stools if the bile was drained externally and a lipoid-free diet given. These observations have been amply confirmed and extended by Buerger and Oeter[28] and also by Beumer and Hepner.[29] The latter authors believe that the amount of biliary cholesterol in the stools makes up but a small part of the total. It has long been known that most of the stool cholesterol is a hydrogenated sterol, coprosterol. This is not resorbed. Whether it is hydrogenated before or after excretion is a questionable point. The biliary cholesterol may be absorbed or hydrogenated to the nonresorbable coprosterol in the intestine. The latter possibly takes place from the action of intestinal bacteria. Schoenheimer[30] has demonstrated a large excretion of sterols by the isolated colon of dogs. Similar studies of the secretion of blind loops of the small intestine also yield high sterol contents.[31]

With these points in mind, one must admit that, while the effect of diet or hypercholesteremia on the biliary cholesterol as a factor in gallstone formation cannot yet be said to be settled, the weight of evidence lies on the negative side. The following experimental and clinical observations tend in our opinion to substantiate this view.

EXPERIMENTAL WORK

Studies were first made on dogs, using the two-way fistula described previously by Peyton Rous and his associates. It is important that such a fistula be used in all of these experiments, as not only does simple drainage of the bile cause infection of the liver and hence disturbance in its physiologic action, but the absence of bile in the intestine breaks up the enterohepatic circulation described by Whipple,[32] and the previous work on this subject which was done in a single one-way fistula may be said to have very little value, for our purposes at least.

While it has long been known that absence of bile from the bowel prevents the absorption of fat, the studies of Weiland and Sorge[33]

27. Sperry, W. M.: Lipoid Excretion: IV. A Study of the Relationship of Bile to the Fecal Lipoids with Special Reference to Certain Problems of Sterol Metabolism, J. Biol. Chem. **71**:351, 1926-1927.

28. Buerger, M., and Oeter, H. D.: Ueber den Cholesteringehalt der menschlichen Darmwand, Ztschr. f. physiol. Chem. **182**:141, 1929.

29. Beumer, H., and Hepner, F.: Ueber die Ausscheidungswege des Cholesterins, Ztschr. f. d. ges. exper. Med. **64**:787, 1929.

30. Schoenheimer, R., and von Bedring, H.: Ueber die Exkretion gesättigter Sterine, Ztschr. f. physiol. Chem. **192**:102, 1930.

31. Schoenheimer, R.: Unpublished work.

32. Whipple, G. H.: Bile Salt Metabolism, J. Biol. Chem. **59**:623, 1924.

33. Weiland, H., and Sorge, H.: Untersuchungen über die Gallensäuren, Ztschr. f. physiol. Chem. **97**:1, 1916.

perhaps give a more complete explanation of the phenomenon. They showed that desoxycholic acid has the power to make loose chemical compounds with a number of different fatty acids. The absorption of fat, it has been suggested, may take place by some such mechanism, and therefore the absence of bile acids from the intestine stops this method of rendering these substances soluble.

The two-way fistula that leads from the proximal end of the common duct to the outside, where it may be tapped and specimens secured, and then goes back to the distal end of the common duct has proved in our hands exceedingly difficult to keep in working condition for long periods. However, with care it can be done, and the accompanying tables are illustrations of the results of such studies.

TABLE 1.—*Effect of Diet on the Bile Cholesterol of Dog 223* *

			Cholesterol, Mg. per 100 Cc.	Bile Salts, Mg. per 100 Cc.	Ratio of Bile Salts to Cholesterol
	5/ 6/31	Gallbladder specimen removed at operation	68.18	4796.5	70.5
1	5/ 6/31	Immediate postoperative specimen.....	27.0	588.2	21.7
2	5/ 7/31	Fed ordinary meat diet; then drained for 4 hours	11.7	269.1	23.0
3	5/ 8/31	Fed ordinary meat diet; then drained for 4 hours	41.6	1063.87	25.5
4	5/ 9/31	Given 100 cc. olive oil by stomach tube; then drained for 4 hours	19.7	1425.4	72.3
5	5/11/31	Given 100 cc. olive oil and 100 cc. cream by tube; then drained 4 hours	21.8	1312.2	60.1
6	5/12/31	Given 100 cc. cream; then drained for 4 hours	10.5	1221.7	116.3
7	5/18/31	Fed 2 Gm. bile salts; then drained for 4 hours	21.4	1380.0	64.4
8	5/19/31	Fed 2 Gm. bile salts; then drained for 4 hours	21.1	1561.0	74.0

* The two-way fistula of McMaster was used, the bile being returned to the bowel after sampling.

Dog 223 (table 1).—The points to be noted here are: First, the wide fluctuations in the cholesterol content in the bile here were due to entirely extraneous influences. The first postoperative specimen taken when the liver was still under the influence of the anesthetic throughout our series showed wide fluctuations in both man and animals. In two cases in human beings reported in a previous paper [34] the cholesterol under these conditions was exceedingly low, falling almost to zero. This was true in some of our dogs, and again in others it tended to run unusually high. We suggest the possibility that dehydration due to operative hemorrhage may have been a factor. The important thing, however, to be noted is the fact that the administration of large amounts of fat has certainly not given the effect of increasing the bile cholesterol. Meat, regarded by some as a precursor of cholesterol, also had no effect. This has been true through our series. In the latter part of the

34. Andrews, Hrdina and Dostal (footnote 1, second reference).

experiment very large amounts of bile acids were fed by mouth, and these also produced no apparent effect on either the cholesterol or the bile acid content of the bile, both of which remained within normal physiologic limits. It was thus possible that the presence of larger amounts of bile acid in the intestine hastened the absorption of cholesterol, which may indeed be the case although it is not reflected in an increased biliary cholesterol. Unfortunately, no studies of the blood cholesterol were made concurrently. The bile salt-cholesterol ratio in

TABLE 2.—*Effect of Diet on the Bile Cholesterol of Dog 167* *

		Cholesterol, Mg. per 100 Cc.	Bile Salts, Mg. per 100 Cc.	Ratio of Bile Salts to Cholesterol	Calcium, Mg. per 100 Cc.
4/15/31	Immediate postoperative specimen...............	15.9	828.21	51.8	5.0
4/16/31	No food postoperatively; bile drained for 4 hours	13.5	757.0	44.6	7.4
4/17/31	Olive oil, 250 cc., by stomach tube; then drained for 4 hours	20.0	1078.0	53.0	5.8
4/20/31	A.m.: dog fasting; drained for 4 hours..........	36.5	1439.0	39.0	12.5
4/20/31	P.m.: 500 Gm. bread and 100 cc. Karo syrup; drained for 4 hours	54.5	858.3	15.0	6.75
4/21/31	Fed 500 Gm. lean meat; drained for 4 hours.....	31.5	1391.0	44.0	12.6
4/22/31	No feeding; bile drained for 4 hours.............	18.0	1357.0	74.0	13.9
4/24/31	No feeding; bile drained for 4 hours.............	7.4	1123.0	150.0	....
4/24/31	Olive oil, 300 cc., by stomach tube; drained for 4 hours	8.6	532.0	62.0	8.8

* The two-way fistula of McMaster was used, the bile being returned to the bowel after sampling.

TABLE 3.—*Effect of Diet on the Bile Cholesterol of Dog 180* *

		Cholesterol, Mg. per 100 Cc.	Bile Salts, Mg. per 100 Cc.	Ratio of Bile Salts to Cholesterol	Calcium, Mg. per 100 Cc.
4/22/31	Immediate postoperative specimen...............	9.5	939.5	98.6	11.45
4/23/31	No feeding; bile drained for 4 hours.............	12.5	689.9	55.2	12.7
4/24/31	A.m.: stock diet fed the night previously; drained for 4 hours	8.0	158.8	79.4	9.2
4/24/31	P.m.: 300 cc. olive oil by stomach tube; drained for 4 hours	10.0	527.3	52.7	9.4
4/25/31	Stock diet fed the night previously; drained for 4 hours	18.4	.....	....	....

* The two-way fistula of McMaster was used, the bile being returned to the bowel after sampling.

dog liver bile runs from 50 to 150, averaging around 100. During the first postoperative day or two the ratio as shown here was quite low, lying in the range of normal levels in human beings. However, we attached no significance to this fact whatsoever, as it was shown in a previous paper that under influences of liver poisons much of the bile acids is excreted in an uncombined form which would not show in the amino-nitrogen method of Van Slyke, which was used throughout.[34]

Dog 167 (table 2).—The same features were obvious throughout this experiment. There was no effect whatsoever from the administration of fatty foods. In fact, the lowest bile cholesterol found was after

the administration of large amounts of olive oil. Here again a factor is evident that McMaster [11] had noted; that is, that the biliary cholesterol is raised by starvation far more than by any other means. The bile salt-cholesterol ratio runs in the usual range except during the first few days after operation, when it is apparently disturbed by the factors already mentioned.

Dog 180 (table 3).—Here again the total dissociation of fatty food from bile cholesterol is obvious, and the bile salt-cholesterol ratio remained within the normal limits for this type of animal throughout the experiment.

Table 4 is put in simply to show cholesterol values in postoperative specimens and well illustrates the wide variation found in these early

TABLE 4.—*Early Postoperative Bile Cholesterol: the Effect of Ether*

Rous Double Fistulas	Mg. of Cholesterol per 100 Cc. of Bile
Dog 177.......{First postoperative specimen........................	14.2
Second postoperative specimen.............	22.0
Third postoperative specimen...........	33.3
	42.1
Dog 232........First postoperative specimen...............	28.0
Dog 293...... {First postoperative specimen.............................	14.2
Second postoperative specimen...........	23.0
Dog 281........First postoperative specimen...........	10.7
Case 9658.....(Human being)	8.40
Case 34963....(Human being)	48.0
Case 36958....(Human being)	4.73

specimens. Whether it is related to starvation or not is difficult to tell, but it is a fact that in certain cases following operation bile containing an unusually large amount of cholesterol may be excreted.

CLINICAL DATA

Table 5 is illustrative of a carefully controlled experiment on a human being with a common duct tube from which all the bile was drained; the observations were continued for nineteen days. This is the same case part of the data from which was reported in the second paper of this series.[1] The patient had diabetes of mild degree, well controlled before operation. During the first few days after operation she had a slight glycosuria with some acidosis, but she rapidly returned to normal and was able to eat a normal diet during the last fourteen days of the experiment. While unfortunately no studies were made on the blood cholesterol, one would certainly expect somewhat of a lipemia in such a case. It is obvious from the chart and table 5 that if this was present it was not reflected by increased excretion in the bile.

The diet was rapidly increased to normal on the first four post-operative days, and from then on the patient received 130 Gm. of fat per day. On the twelfth to fifteenth day this diet was cut down to 50 Gm. of fat per day, and again it can be seen that this had no effect on the biliary cholesterol. During each of the periods noted she had

TABLE 5.—*Complete Record on Fistula Bile in Patient E. C.*

No.	Time	Volume, Cc.	Total Solids, Gm.	Cal-cium, Mg. per 100 Cc.	Choles-terol, Mg. per 100 Cc.	Bile Salts as Glyco-cholate, Mg. per 100 Cc.	Comment
1	1st postoperative hr.	15	3.51	6.45	48.0	6	
2	Next 18 hours	250	3.43	7.7	58.8	47	
3	8 a.m. to 4 p.m.	46	1.99	6.0	50.0	0	
4	4 p.m. to 12 n.m.	95	1.98	5.35	51.2	0	
5	12 n.m. to 8 a.m.	108	1.79	4.6	47.5	0	
6	8 a.m. to 4 p.m.	124	1.50	4.7	48.1	6	
7	4 p.m. to 8 n.m.	158	2.13	4.1	54.5	0	
8	8 n.m. to noon	28	2.11	5.0	62.4	22	8 a.m.: dehydrocholic acid, 0.5 Gm.
9	Noon to 8 a.m.	145	2.80	5.35	82.1	20	
10	8 a.m. to noon	15	....	7.34	62.4	35	8 a.m.: desoxycholic acid, 0.5 Gm.
11	Noon to 8 a.m.	200	2.43	7.1	52.8	57	
12	8 a.m. to noon	20	....	7.7	50.8	44	8 a.m.: dehydrocholic acid, 0.5 Gm.; cholesterol, 1 Gm.
13	Noon to 8 a.m.	180	3.46	7.5	65.0	13	
14	8 a.m. to noon	45	2.62	6.9	58.0	42	
15	Noon to 8 a.m.	200	3.47	7.9	73.0	51	
16	8 a.m. to noon	60	3.99	7.1	69.0	0	
17	Noon to 8 a.m.	500	2.10	6.2	83.0	20	
18	8 a.m. to noon	45	2.56	7.2	51.0	66	8 a.m.: desoxycholic acid, 0.5 Gm.; cholesterol, 1 Gm.
19	Noon to 8 a.m.	200	3.38	8.3	81.0	47	
20	8 a.m. to noon	30	....	8.3	58.0	103	8 a.m.: dehydrocholic acid, 0.5 Gm.
21	Noon to 8 a.m.	195	2.98	6.9	75.0	22	
22	8 a.m. to noon	45	3.16	8.7	56.0	70	8 a.m.: dehydrocholic acid, 0.5 Gm.
23	Noon to 8 a.m.	260	3.37	6.9	83.0	72	
24	8 a.m. to noon	150	2.49	8.3	67.0	42	8 a.m.: dehydrocholic acid, 0.5 Gm.; cholesterol, 1 Gm.
25	Noon to 8 a.m.	350	2.44	7.1	56.0	46	
26	8 a.m. to noon	105	2.82	6.8	76.0	11	8 a.m.: cholesterol, 1 Gm.
27	Noon to 8 a.m.	355	2.50	6.7	66.0	46	
28	8 a.m. to noon	125	2.41	5.5	60.0	18	8 a.m.: cholesterol, 1 Gm.
29	Noon to 8 a.m.	415	2.45	7.1	58.0	25	
30	8 a.m. to noon	65	2.92	7.9	71.0	32	8 a.m.: cholesterol, 1 Gm.
31	Noon to 8 a.m.	550	2.72	6.6	67.0	45	
32	8 a.m. to noon	150	2.05	5.6	58.0	0	8 a.m.: cholesterol, 1 Gm.
33	Noon to 8 a.m.	445	2.08	5.5	71.0	15	
34	8 a.m. to noon	125	2.35	5.5	49.0	0	
35	Noon to 8 a.m.	350	2.50	6.0	78.0	11	
36	8 a.m. to noon	75	2.35	5.3	57.0	11	
37	Noon to 8 a.m.	365	2.50	5.9	63.0	11	
38	8 a.m. to noon	140	1.92	4.6	62.0	11	
39	Noon to 8 a.m.	325	2.41	4.7	65.0	0	

received doses of bile salts by mouth which should have aided in the absorption of fat.

During the course of the experiment, cholesterol was administered by mouth on various occasions, as were bile acids and both substances together. In each case these were given at 8:00 a. m., and the subsequent four hour specimen of bile was analyzed separately from the rest of the twenty-four hour specimen. During the entire period here

reported the stools were free from bile. The cholesterol was dissolved in butter which was allowed to harden again before feeding. This is quite necessary, as crystalline cholesterol is often not absorbed. The dose in each case was 1 Gm. The bile acids used were desoxycholic and dehydrocholic, in doses of 0.5 Gm. in several capsules. It is important to use the acids and not the sodium salts, which are much more disagreeable to taste. The patient was afebrile during the experiment, and was able to take fluids freely, so that dehydration was not a factor. All the ingested food and drugs were retained, there being no vomiting.

The data gathered in the studies may be summarized as follows:

1. As already noted, the fact that the patient had diabetes did not bring about an increase in the amount of cholesterol in the bile either in the concentration or in the daily output.

2. Variations in the dietary fats and proteins had no effect on the biliary excretion. While it has been noted by various observers [35] that the blood cholesterol is affected by diet only slowly and over long periods, one would expect a nineteen day study of this type to have some effect on the bile, even allowing for the slowness of the response.

3. The feeding of cholesterol, even when accompanied by bile acids, likewise had no effect whatsoever.

4. The feeding of bile acids, desoxycholic or dehydrocholic, either alone or with cholesterol, had no effect on the bile cholesterol. Theoretically these must have materially hastened the absorption of fats and raised the blood cholesterol, and we regret that this was not studied.

5. No correlation between the cholesterol and the total solids of the bile could be found.

6. No relation existed between the cholesterol content and the volume of bile excreted.

7. The constancy of the bile cholesterol here as well as in other experiments in human beings previously reported is remarkable. In this case in spite of all the changes in the experimental conditions, it varied only between 55 and 75 mg. per hundred cubic centimeters. In our hands the colorimetric estimation has never been perfected to the same degree of accuracy reported by several other observers. With our most carefully made tests the margin of error has proved to be at least 15 per cent. From this it may be seen that the fluctuations within the range reported may be mostly experimental error. In dogs the range of normal fluctuation is often much greater than in man.

The accompanying chart is composed of the same data plotted to represent in milligrams per hour the excretion of both bile salts and

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35. Fox (footnote 21). Gardner and Gainsborough (footnote 22). Gainsborough (footnote 23).

cholesterol. When plotted in this manner it is evident at once that the fluctuations are considerably greater. However, careful examination of the chart again confirms the fact that there is no correlation whatsoever between the excretion per hour of cholesterol and (1) diet, (2) the oral administration of cholesterol and (3) the oral administration of bile acids.

After a postoperative period with very small cholesterol excretion, it reaches a level which it tends to maintain entirely free from dietary
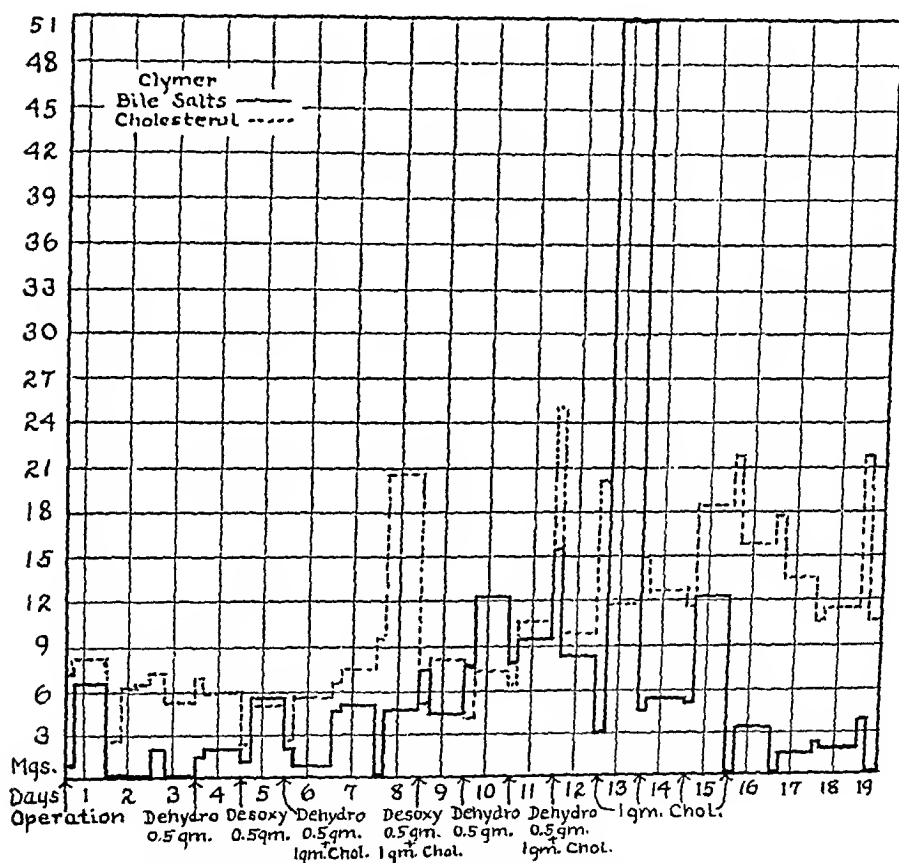
Same data as tabulated in table 5, calculated in milligrams per hour. Note the complete dissociation of the diet and feeding of cholesterol or bile salts from the excretion of either in the bile.

influence. One of the most striking phenomena noted was the fact that the cholesterol excretion was so much higher in the morning specimens throughout. It averaged 18 mg. per hour, and then 12 mg. per hour during the rest of the day, a 50 per cent increase. Fasting is probably the explanation of these results. The total cholesterol found in the bile during the last ten days of the experiment, after the postanesthetic period was over, was only about 3 Gm. This is in marked contrast to

the fact that the patient received 6 Gm. of pure cholesterol by mouth besides the considerably larger amount that was contained in the high fat diet given for diabetes. This appears to confirm in man the observations of Schoenheimer on dogs, that the major share of cholesterol is excreted by the mucosa of the bowels. It is unthinkable that such a large amount is stored daily, even with a bile fistula. Of course, it may be that the meager amount of bile salts provided (3.5 Gm.) was not enough to permit the absorption of so much lipoid material.

COMMENT

Gardner and Gainsborough,[22] in their recent studies on blood cholesterol, not only agreed with Campbell in totally dissociating it from the problem of gallstone formation [6] but also showed that the previous conceptions of biliary obstruction and cholesterol were at fault. They quite conclusively demonstrated that in biliary obstruction there is not a rise but a marked fall in the sterol content of the blood. This fall, which also occurs after fistula formation, is in the ester fraction and is due to failure of absorption from the intestine. It is only after prolonged jaundice that a rise in the blood cholesterol occurs. The following quotations from their conclusions is quite in accord with our findings:

> The usual theory that this change is due to retention in the blood of cholesterol from the bile is quite inadequate. . . . Hypercholesterolemia does not occur in uncomplicated cholelithiasis. . . . There is no evidence that the cholesterol content of the food influences the cholesterol content of the bile or has any relation to gall stone formation. . . . The marked hypercholesterolemia, which occurs in some forms of nephritis, also does not lead to any increase in incidence of cholelithiasis.

CONCLUSIONS

1. The cholesterol content of the bile is independent of dietary factors.

2. In these studies no changes in the bile salt-cholesterol ratio of sufficient magnitude to approach the critical level for precipitation have been found. The responsibility for gallstone formation seems to lie in the gallbladder rather than the liver.

HEALING OF FRACTURES, OF DEFECTS IN BONE AND OF DEFECTS IN CARTILAGE AFTER SYMPATHECTOMY

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In this article we wish to report the results of experiments performed in an attempt to determine whether or not sympathectomy influences the healing of cartilage and bone.

HEALING OF FRACTURES AND OF BONE DEFECTS AFTER SYMPATHECTOMY

The Literature.—Physiologists have demonstrated repeatedly that removal of the sympathetic ganglions supplying a limb is followed by a dilatation of the blood vessels and increased flow of blood through that limb. Furthermore, certain investigators have maintained that an identical result is secured by the removal of a segment of the outer coat of the main artery. These developments have led clinicians to the use of one or another of these procedures in the treatment of almost every pathologic condition that might possibly be attributed to a deficiency in local circulation. One of these conditions is the state of delayed union or nonunion in fractures of the bones of the extremities.

The first use of sympathectomy in the treatment of delayed union of fractures was by Kappis[1] in 1923. He performed periarterial sympathectomy of the femoral artery of a man, aged 23, who had had a fracture of both bones of the leg about ten weeks before. The fracture had been treated by open reduction followed by skeletal traction and a plaster cast. The periarterial sympathectomy was followed by rapid union, and the fracture was healed within six weeks after the operation on the artery. In 1924, Füth[2] reported two similar cases, and two more cases were reported by Rubaschow[3] in 1925. Other cases of the same

1. Kappis, Max: Further Experiences with Periarterial Sympathectomy in Delayed Union, Klin. Wchnschr. 2:1441, 1923.

2. Füth: Ber. a. chir. Gesellsch., November, 1924, p. 61.

3. Rubaschow, S.: Periarterial Sympathectomy in Delayed Union of Fractures, Zentralbl. f. Chir. 52:635, 1925.

type have been reported by Gaudier,[4] Fontaine,[5] Stropeni,[6] Estor [7] and Floresco.[8] Uffreduzzi [9] made the statement that in delayed union when the delay is not due to mechanical influences, the indication for periarterial sympathectomy is perfect.

It is to be noted that all of the foregoing observations are in clinical cases, and that, with the exception of Fontaine, no author reported more than three cases. Fontaine reported eight cases, and in four of these sympathectomy appears to have been followed by definite benefit, while in four others there was no apparent benefit from the operation. In fact, in one case a low grade infection seems to have been aggravated.

Palma [10] reported experimental work in which he removed the lower cervical sympathetic ganglion on one side and fractured the radius on both sides in six rabbits. The animals were killed on the fifth, tenth, fifteenth, twentieth, thirtieth and forty-fifth days. Roentgen and microscopic examination of the fractures showed much more rapid consolidation of the fractures and disappearance of the callus in the sympathectomized limb. He believed that the more rapid union on the sympathectomized side was due to the increased blood flow in the area and considered his experimental results as proof of the importance of the blood supply in the repair of fractures. Fontaine [5] performed bilateral osteotomies of the metatarsals of dogs and periarterial sympathectomy on one side and noted more rapid union on the sympathectomized side. Gaudier [4] performed experimental periarterial sympathectomy in dogs and reported that in spite of the difficulty of the operation on small vessels there was more rapid healing in fractures of limbs that had been subjected to the sympathectomy. Unfortunately, Gaudier does not give the details of his experiments. Pearse and Morton [11] removed the sympathetic ganglions and chain from the renal vein down to the sacrum on the left side in ten dogs and resected uniform segments of the fibulae in the same animals. They were able to detect little, if any,

4. Gaudier, H.: Periarterial Sympathectomy and Fractures of the Extremities, Bull. et mém. Soc. nat. de chir. **52**:1190, 1926.

5. Fontaine, R.: Eight Cases of Retarded Consolidation and Pseudarthrosis Treated by Periarterial Sympathectomy, Rev. de chir. **64**:95, 1926.

6. Stropeni, L.: Periarterial Sympathectomy to Promote Healing of Fractures, Arch. ital. di chir. **15**:601, 1926.

7. Estor, E.: Sympathectomy and Fractures of the Extremities, Bull. et mém. Soc. nat. de chir. **53**:647, 1927.

8. Floresco, A.: A Case of Pseudarthrosis of the Forearm Healed by Periarterial Sympathectomy, Rev. d'orthop. **16**:503, 1929.

9. Uffreduzzi, Ottorino: A Study of the Physiopathological and Clinical Periarterial Sympathectomy, Gaz. d. hôp. **101**:265, 1928.

10. Palma, R.: Influence of Sympathectomy on the Process of Reparation of Fractures Through Animal Experiments, Ann. ital. di chir. **4**:85, 1925.

11. Pearse, H. E., Jr., and Morton, J. J.: The Influence of Alterations in the Circulation of the Repair of Bone, J. Bone & Joint Surg. **13**:68, 1931.

difference in the healing on the two sides and concluded that the sympathetic system has little influence on osteogenesis.

Materials and Methods.—These experiments were performed on cats, and the procedure consisted of resection on the right side of the stellate (first thoracic) ganglion and the two subjacent thoracic (second and third) sympathetic ganglions. Since all of the sympathetic preganglionic fibers leave the cord to enter the chain at or below the first thoracic segment, this operation not only destroys the sympathetic components of the first and second thoracic spinal nerves, but also interrupts the sympathetic component to all cervical nerves and is thus a complete sympathectomy for the fore leg (Ranson [12]). At intervals of from one to two weeks after the sympathectomy, transverse osteotomy of the ulna of each fore leg was performed, thus giving uniform fractures on the right sympathectomized side and on the left normal side, the latter serving as a control. The animals were then killed at intervals of from nineteen to seventy-four days after the osteotomies. At autopsy, the ulna and radius were removed, examined in the gross and then fixed in formaldehyde. X-ray photographs were made, and the bones were then decalcified, sectioned, stained in hematoxylin and eosin and studied microscopically.

In addition to the foregoing, a large rectangular defect, approximately 1.5 cm. long and including approximately half of the shaft of the ulna, was created in each fore leg of one animal in which the right upper thoracic sympathetic ganglions had been removed as described.

Results.—The fractures on both the control and the sympathectomized side appeared to heal at approximately the same rate. That is, by gross examination, x-ray photographs (fig. 1) and microscopic examination we were not able to detect any difference between the healing of fractures in the sympathectomized and the nonsympathectomized extremities. The same was true of the bone defect. On microscopic examination, there appeared to be considerable vascular dilatation in the region of the fracture in some of the sympathectomized limbs, but the same was true of the vessels in the vicinity of the fractures in the control limbs of the same animals.

It is further to be noted that the operation of sympathectomy was not followed by any demonstrable difference in the bones of the extremity which were not operated on. If it is true that increased circulation leads to absorption of bone (Leriche and Policard [13]), we

12. Ranson: An Introduction to a Series of Studies on the Sympathetic Nervous System, J. Comp. Neurol. **29**:305, 1918. Ranson and Billingsley: The Superior Cervical Ganglion and the Cervical Portion of the Sympathetic Trunk, ibid. **29**:313, 1918.

13. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone, St. Louis, C. V. Mosby Company, 1928.

should find atrophy of all of the bones of the sympathectomized extremities. However, careful study of these bones by roentgen and microscopic examination failed to reveal any difference in density between those of the sympathectomized and the control limb.

HEALING OF CARTILAGE AFTER SYMPATHECTOMY

The Literature.—In 1927, Rowntree and Adson [14] reported observations on cases of chronic "infectious" arthritis after sympathectomy. The advisability of this operation is still *sub judice;* however, the authors believe that in certain carefully selected cases of chronic
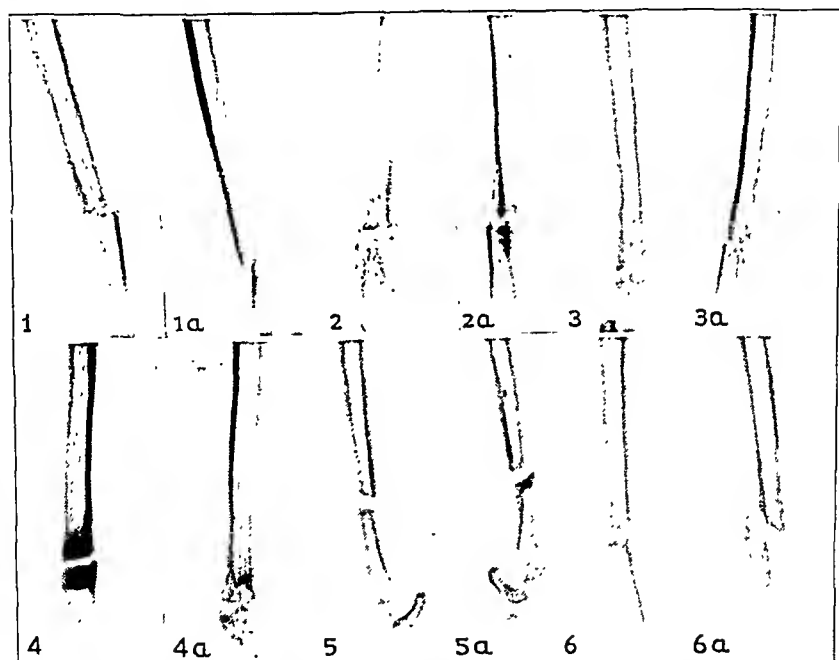
Fig. 1.—Here are shown x-ray photographs of the ulnae of cats after osteotomies (in each instance the figure on the left is from the sympathectomized limb and the one on the right is from the control): *1*, nineteen days; *1 a*, control. *2*, thirty-five days; *2 a*, control. *3*, forty-one days; *3 a*, control. *4*, fifty-one days; *4 a*, control. *5*, sixty-four days. *5 a*, control. *6*, seventy-four days; *6 a*, control.

"infectious" arthritis sympathectomy is indicated and offers a chance of considerable improvement in cases that have not responded to other forms of treatment (Hench, Henderson, Rowntree and Adson [15]).

14. Rowntree, L. G., and Adson, A. W.: Bilateral Lumbar Sympathetic Ganglionectomy and Ramisectomy for Polyarthritis of the Lower Extremities, J. A. M. A. **88**:694 (March 5) 1927.

15. Hench, P. S.; Henderson, M. S.; Rowntree, L. G., and Adson, A. W.: The Treatment of Chronic "Infectious" Arthritis by Sympathetic Ganglionectomy and Trunk Resection, J. Lab. & Clin. Med. **15**:1247 (Sept.) 1930.

Their observations were limited to clinical cases because the cause of chronic arthritis is still unknown and the typical disease has not yet been produced in experimental animals (Key [16]). Consequently, it is not possible to determine in experimental animals the effect of any form of therapy on this condition.

However, one of us (Key [17]) has shown that if a rectangle of the articular cartilage is removed from the patellar surface of the femur of rabbits, in a large percentage of the animals a chronic progressive
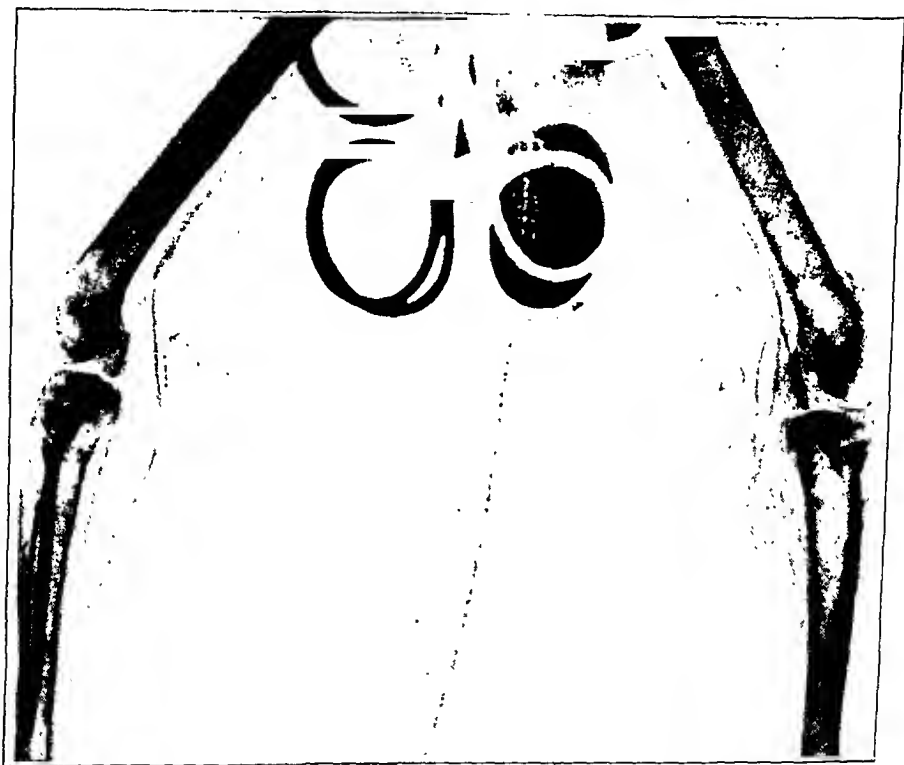
Fig. 2.—X-ray photograph of the hind limbs of a living cat taken after the injection of 1.5 cc. of 100 per cent sodium iodide into the abdominal aorta. Ten weeks previously a left lumbar sympathectomy had been done. The arterial system of the left limb is still greatly dilated as compared with that of the right.

arthritis will develop in the knee operated on. Consequently, it was decided to determine the effect of sympathectomy on this type of experimental arthritis.

16. Key, J. A.: Pathogenic Properties of Organisms Obtained from Joints in Chronic Arthritis, Proc. Soc. Exper. Biol. & Med. **26**:863, 1929.

17. Key, J. A.: Experimental Arthritis: The Changes in Joints Produced by Creating Defects in the Articular Cartilage, J. Bone & Joint Surg. **13**:725 (Oct.) 1931.

Materials and Methods.—In this series of experiments a rectangle of cartilage approximately 3 by 5 mm. was removed from the patellar surface of the femur in each knee joint of a series of thirteen cats. Either at the time of the operation on the knee or from one to two months later, left lumbar sympathectomy and splanchnotomy were performed on these animals. They were then killed at intervals of from six to twelve months after the operation on the knee, and the knee joints were studied in the gross and microscopically.

Results.—As well as we could determine by gross and microscopic examination, the cartilage healed in practically the same manner and at practically the same rate in the sympathectomized limb and in the control joint of the other leg of the same animal. In all of these animals the defect tended to heal by fibrous tissue, and in some instances partly by regeneration of the cartilage, and there was no evidence of the expected chronic arthritis developing in any of the cats such as one of us (Key) has described in rabbits after similar defects in the articular cartilage.

<div align="center">COMMENT</div>

It has been demonstrated (Moore, Williams and Singleton [18]) that lumbar sympathectomy and splanchnotomy as performed by us result in a vasodilatation in the corresponding hind leg which lasts for at least ten weeks and which is sufficiently marked to be visualized in x-ray photographs of both hind legs taken after a 100 per cent solution of sodium iodide has been injected into the abdominal aorta (fig. 2). It is thus evident that the operation as performed on our animals is an adequate test as to whether or not sympathectomy influences the healing of cartilage in the extremities operated on.

We were led to perform these experiments on cartilage largely because of our interest in chronic arthritis. It has been shown by one of us (Key) that if a rectangular defect is created in the cartilage on the patellar surface of the femur in rabbits, these animals may be expected to develop a progressive chronic arthritis in the joints operated on. Much to our surprise, none of the cats operated on developed arthritis. At the present time we are not able to explain this difference in reaction between the two animals. It cannot be explained on a basis of the rabbits being more active, because the cats were all kept together in a large cage and their activity was in no way restricted. It is possible that diet may have something to do with it, as the cats were fed an almost pure meat diet while the rabbits were fed a vegetable diet, but it is probable that the joints of rabbits are merely more liable to undergo pathologic changes than are those of cats.

18. Moore, R. M.; Williams, J. H., and Singleton, A. O., Jr.: The Peripheral Course of Vasoconstrictor Fibers as Revealed by a Radiographic Method, Arch. Surg., this issue, p. 308.

We have been able to produce a similar, though less marked, arthritis in dogs by the creation of defects in the articular cartilage. Thus it is seen that dogs occupy a place midway between cats and rabbits. We expect to try out the effect of sympathectomy on rabbits and dogs in which defects have been created in the cartilage of both knees in order to determine whether or not sympathectomy has any influence on the production of the arthritis.

At present our experimental observations offer no support for, or evidence against, the use of sympathectomy in the treatment of chronic arthritis. However, in the experimental animals we could detect no difference between the joints of the sympathectomized limbs and those of the controls on the other sides of the same animals.

In our experiments on bone healing we first resected portions of the fibula and bored holes in the tibia in the legs of cats that had been subjected to abdominal sympathectomy. These experiments gave negative results. However, the fibula is such a small bone that we did not consider the negative results as of much value. Likewise, the healing of the drill holes in the tibia were not considered an adequate test as to whether or not sympathectomy might influence osteogenesis. Consequently, we were forced to perform our operations on the bone on the fore leg, as it was necessary to have an adequate control on opposite sides and the fore leg is the only place in an animal where it is possible to operate on a relatively large bone on both sides and have adequate splintage and no crippling.

Unfortunately, the sodium iodide method was not applicable for controlling the effect of sympathectomy on the blood vessels in the fore leg. The iodide is quite toxic to the nerve centers, and the animal survives its presence in the abdominal aorta only while the aorta and the vena cava are clamped above the site of the injection. It is not possible to make a simultaneous injection into both fore legs without permitting the sodium iodide to enter the central nervous system, and this causes death of the animal and vitiates the result. However, since it has been demonstrated that the operation as performed severs all of the sympathetic fibers to the fore leg (Ranson) there is no doubt but that our experiments have been adequate to produce vasodilatation in the sympathectomized limb.

Our experiments demonstrate that in normal animals with fresh fractures sympathectomy that results in prolonged dilatation of the blood vessels of the limb operated on has no influence on the healing of fresh fractures and bone defects, but this does not rule out the possibility that sympathectomy may not be of value in some cases of delayed union. However, this has yet to be demonstrated in other than clinical observations which are open to question because they are not controlled. In a case of delayed union it is rarely possible to say

whether nonunion will or will not occur. Likewise, it will be difficult to prove this point experimentally, because in experimental animals in which large defects sufficient to cause nonunion are created our observations reveal no probability that sympathectomy may stimulate osteogenesis and cause union to occur.

CONCLUSIONS

1. Sympathectomy has no influence on the healing of fresh fractures or fresh bone defects.

2. Sympathectomy has no influence on the healing of defects in articular cartilage.

RÔLE OF INFECTION IN THE PRODUCTION OF POSTOPERATIVE ADHESIONS

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The occurrence of omental and intestinal adhesions after laparotomy has been a source of trouble ever since asepsis permitted the surgeon to open the peritoneum, and frequently these adhesions give rise to more acute symptoms than the condition for which the operation was done. At first adhesions were recognized only by the occurrence of intestinal obstruction, but later surgeons noted that a picture of dull, dragging pain or of partial obstruction after a laparotomy was the result of the presence of omental bands and intestinal adhesions.

Many theories have arisen as to the etiologic factors concerned in the production of adhesions, although little experimental work has been done. Every surgeon is familiar with the protective action of omentum and of fibrinous exudate in the walling off of infection or perforation. Without this protective action, the mortality resulting from many procedures would be considerably greater than it is. It is only when these adhesions form in excessive amount, fail to absorb or form in detrimental positions that they lose their beneficial properties and become a menace to health and to the success of the operation performed. Thus in many instances adhesions of omentum that successfully wall off a ruptured appendix after operation may cause symptoms and even obstruction at a later period. Moreover, the question has often arisen as to why among persons subjected to similar technics and similar operative procedures symptomatic adhesions should develop in a certain number while others are free from them.

Infection and trauma have long been conceded to be important factors in the production of adhesions, and the etiology of the early or protective adhesions seems generally accepted as being due to these factors. The cause of the hardened or detrimental adhesions is much less understood. Factors of origin, of reabsorption and of disappearance enter into the question, and make the etiology even more complicated.

From conjecture and experimental evidence two conclusions seem possible: that adhesions are primarily formed by trauma on which irrita-

tion by chemicals or bacteria is superimposed, and that the further processes of absorption are by means of phagocytosis and the action of proteolytic enzymes. We have as yet no means to determine why resolution occurs in some early adhesions while others develop into hard and detrimental types, nor can we explain the adhesions occurring in the so-called "clean" cases in which aseptic technic is used, since trauma alone, unless severe enough to admit bacterial contamination, will not produce adhesions.

The mechanism of production, the morphology and the development of abdominal adhesions have been so well described by Ladwig [1] in a recent article that additional details would be almost superfluous. His study explains many of the phases of adhesions noted clinically—in the formation, resorption, late disappearance and reformation after release by operation. Thus the readiness with which early and fresh adhesions may be broken up and their readiness to hemorrhage are easily understood from his description of the early adhesion in which are found many blood vessels with little fibrous or fibroblastic material, but much fibrin, exudate and edema with fatty tissue as a network. The later firmness of adhesions is readily explained by the additional presence of collagenous and elastic fibers, which occur only in certain adhesions, while others remain in the network stage or recede. Finally, the fact that real symptoms occur at various intervals after formation of these adhesions is explained by the contraction and condensation of these fibers, but much more by the results of repeated trauma to adhesions, which causes regrowth of more and more fibrous tissue. Ladwig has demonstrated old and organizing blood clots and nests of fibroblasts in old adhesions which suggest strongly the effect of repeated strains or trauma to the adhesions. This explains, too, the tendency of symptoms of adhesion to exacerbate rather than to decrease or disappear. If the trauma is severe enough, adhesions of this type may conceivably be torn free and the symptoms disappear. According to Ladwig's work, therefore, the adhesions of protection are the adhesions of the first stage of exudate, fibrin and edema, and all further stages are of no value or are malignant in action.

Ladwig further gave basis to explanations of resorption, in the demonstration of phagocytic action and even necrosis in first stage adhesions. He expressed the belief that proteolytic or autolytic enzymes are also present to cause the resorption of the adhesions. Recurrence of adhesions may also be explained by the presence of the nests of fibroblasts in old adhesions which are stimulated by any further trauma.

Basing our views on the fact that adhesions are found in almost all cases of infection of the peritoneum, we felt that infection was the

1. Ladwig, A.:   Arch. f. klin. Chir. **151**:1, 1928.

primary factor even in the so-called "clean" cases. An experiment was accordingly devised to determine the effect of infection of wounds in the production of adhesions in noncontaminated or "clean" cases.

Guinea-pigs were chosen as the experimental animals, partially because of their extremely small and thin omentum and partially because of the lack of adhesions observed during experiments of another type. Thirty guinea-pigs were used, of an average weight of 500 Gm. The abdomen was clipped, shaved and carefully sterilized. An intraperitoneal injection of sodium amytal, shown by Lacey to produce no adhesions, was given to anesthetize the animals. An incision was then made with all sterile precautions, 1 cm. to the right of the midline in the lower right quadrant. The muscles were gently dissected down to the peritoneum. Great caution was taken to prevent opening or traumatizing of the peritoneum. The muscles were gently lifted free from the peritoneum laterally for about 1 sq. cm. In the space was placed a bit of gauze 0.5 cm. square and four layers in thickness. In one series the gauze was sterile; in another it was dipped in 5 per cent tincture of iodine and moderately dried before insertion, and in the final series it was dipped into a twenty-four hour broth culture of Bacillus coli, moderately dried and put into place without coming into contact with any surrounding structures. The muscles were then closed in layers by continuous sutures of 000 chromic catgut, and the skin was closed with silk.

After operation the series with sterile gauze showed some redness of the wound with slight edema and swelling which lasted only from twenty-four to forty-eight hours, the wound then healing uneventfully. The series in which iodine was used showed a more severe reaction, but the wound did not break down or show infection; the redness and swelling increased and disappeared in a week or ten days. The last series, as is to be expected, showed infection and abscess in all but two instances. In three the gauze was completely extruded. The mean reaction consisted of an abscess about 1 cm. in diameter, the center breaking down and healing in three weeks. The most severe reaction was a large abscess about 2.5 cm. in diameter with a crater of 1 cm. This abscess did not heal in eight weeks.

The animals were killed in from eight weeks to three months. The abdomen was opened on the left side, and the abdominal wall gently rolled over to reveal whether adhesions were present. The results were as follows:

	No. of Animals	Adhesions	No Adhesions
Sterile gauze.....................	10	0	10
Tincture of iodine................	10	1	9
B. coli.........................	10	6	4

In each instance except those in which the gauze had been extruded, it was located and found tight against the peritoneum. The adhesion produced by iodine was firm and consisted of omentum. In the final series the seminal vesicle was twice adherent to the scar and the

omentum three times, and in one experiment with a large abscess there were adhesions of the colon, several loops of the small intestine, the liver and the omentum.   Of the four animals in this series in which no adhesions occurred, two had no wound abscess and two had moderate abscesses, one of which had not quite healed in three months.
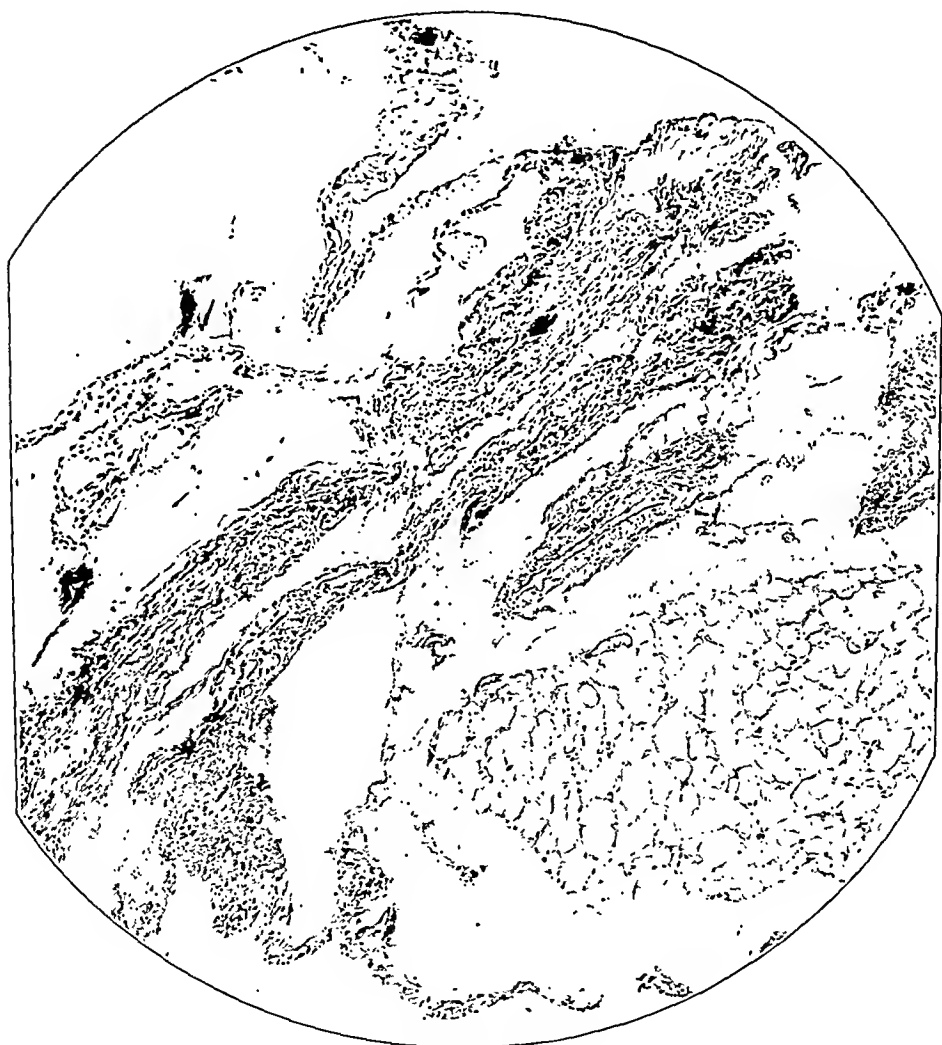
Fig. 1.—Section of human adhesion showing fibrous tissue and network of fatty tissue.

These results seemed to confirm the theory that infection is a large etiologic factor in the production of adhesions, and a survey of clinical cases was then made to trace the influence of this factor.   It was obviously impossible to study the follow-up reports of all laparotomies

and determine accurately the presence or absence of adhesions. The inaccuracy of determining the presence of adhesions alone would make such a survey valueless. We therefore analyzed only those cases in which reoperation was done for symptoms caused by postoperative adhesions. Interviseceral and pelvic adhesions were ruled out and only omental adhesions to the parietal wall were chosen. A total of forty-two
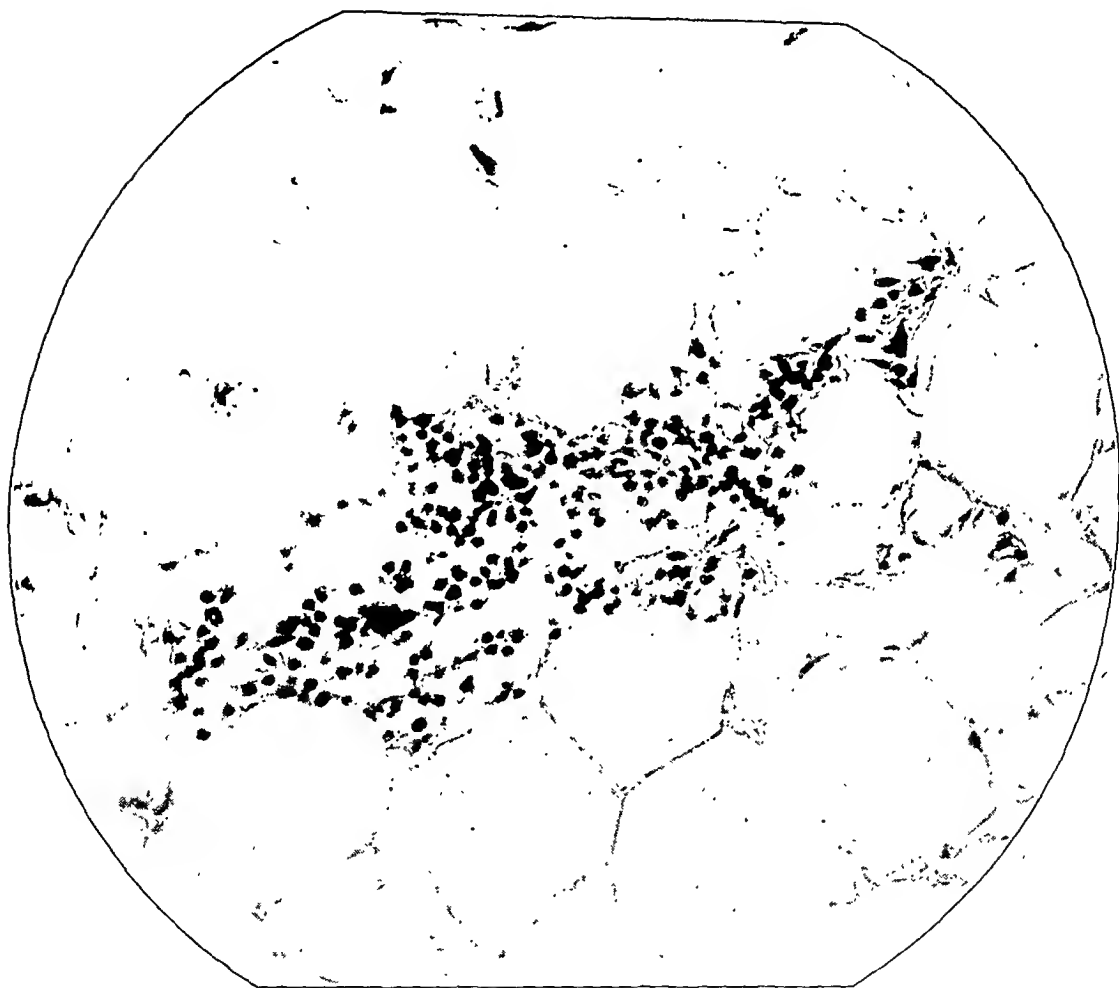
Fig. 2.—Section of human adhesion showing nest of fibroblasts.

cases were reviewed in detail. An accurate history as to infection of the wound and drainage was available in every instance from the records of the previous operation. In thirty-five of this series of forty-two patients operated on for symptoms caused by adhesions, drainage had been used, and in seven the operative procedure did not require drainage. While the use of a drainage tube does not necessarily imply the presence of infection, as in cholecystectomy for instance, the presence of a foreign body by reason of its potential infection from within the abdomen

or retrograde from skin or dressings brings these cases in the infected group. Greater interest lies in the group of seven cases in which the wound was closed without drainage, because in six of the seven the record showed postoperative infection of the wound.
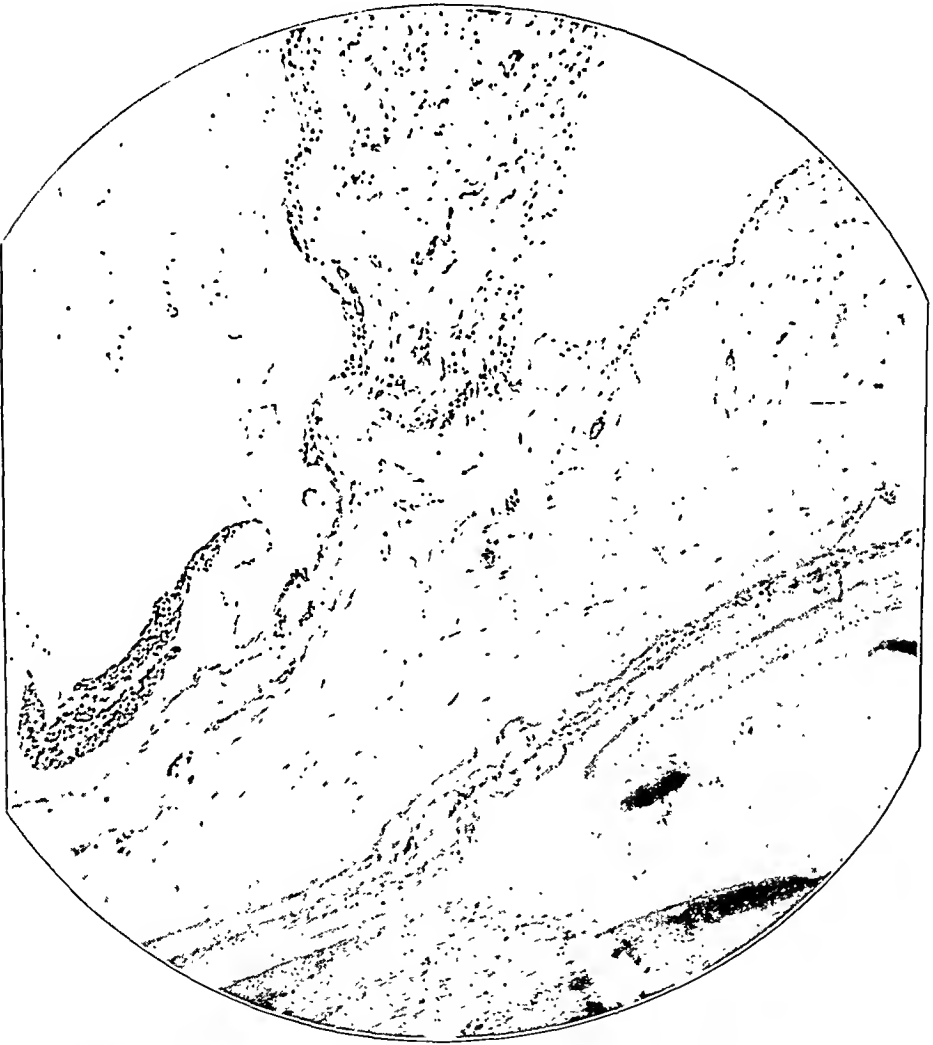
Fig. 3.—Section from animal. Omental adhesion from tincture of iodine at attachment to parietal wall.

Thus in forty-two patients operated on for symptom-producing postoperative adhesions, only one had no drainage or wound infection, and of seven patients without drainage all but one had wound infections. To establish this point further morphologic and cultural studies were made in order to detect the presence of infective agents.

Fig. 4.—Section from animal. Omental adhesion from infection with B. coli, at attachment to parietal wall.

Fig. 5.—Adhesion of small intestine to abdominal wall in severe infection with large abscess.

Sections of human material were made. We could easily demonstrate the network and the collagenous fibers as illustrated in figure 1 and the nests of fibroblasts described by Ladwig (fig. 2), but careful staining and search revealed no micro-organisms. Cultures of tissue removed at operation, immediately immersed in warm saline solution and later transferred to warm bouillon have twice yielded staphylococci in recent adhesions. All other cultures have been negative. The factors of contamination are relatively large in considering absolute bacterial asepsis in the preparation of these cultures, but the positive findings in these two cases may have significance.

Comparison of the structure of the adhesions produced experimentally by iodine and of those produced by infection reveals no fundamental difference, except that the fibers of the infected adhesions go more deeply into the muscle layers of the intestines, and the direct continuity of line is lost by reason of the processes of infection in the overlying muscle layers with their fibrous tissue reaction (figs. 3 and 4). Here again, nests of fibroblasts and fibrous tissue could easily be demonstrated. No bacteria could be demonstrated in sections of animal adhesions when the animals were killed three months after operation; cultures were not made, however.

COMMENT AND CONCLUSIONS

We have presented the point of view that the primary etiologic factor in the production of postoperative adhesions is infection. An experimental study has been cited to confirm this conception. In a clinical survey we have demonstrated that intra-abdominal infection and wound infection are primary factors in causing symptomatic adhesions for which secondary operations are necessary. Finally, the morphologic structure of adhesions has been illustrated.

A NEW SURGICAL PROCEDURE FOR ACUTE PANCREATITIS

REPORT OF SIX CASES

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CASE 1.—The first patient was a man, aged 51, who became acutely ill one day before admission to the hospital and on admission presented an acute surgical abdominal condition with distention, generalized tenderness and rigidity. He was immediately operated on under ether anesthesia. When the abdomen was opened, a large amount of brownish fluid was encountered. Fat necrosis was present, and the pancreas was enlarged and indurated.

The pancreas was drained by the transgastrocolic omental route, from the anterior surface of the pancreas, with a tube drain and a battery of cigaret drains. It drained freely for two days, but on the third day the drainage had practically ceased; under primary ether anesthesia the sinus for drainage was enlarged by blunt dissection, but satisfactory drainage was not obtained. Two days later, under local anesthesia, the gallbladder was drained. The bile was slightly darker than usual, but no stones or other lesions were found. The patient became progressively worse, and expired thirty-six hours later.

This case, as far as I am able to judge from the standpoint of early admission and general physical condition, was the best surgical risk of the series.

Apparently inadequate drainage was the chief cause of failure, although I had provided as much drainage as any textbook that I have seen recommends.

CASE 2.—The second patient was a man, aged 24, who while at dinner was suddenly seized with severe epigastric pain, accompanied by vomiting, chills and perspiration. He was admitted to the hospital the following day at 9 p. m. On admission there was slight distention of the abdomen, with tenderness and moderate rigidity in the epigastrium.

Immediate laparotomy was performed through an upper right rectus incision. There was marked fat necrosis, and the pancreas was definitely enlarged. No associated biliary lesions were found.

This was the first patient in whom the pancreas was drained by the method that will be described later in this paper. There was profuse drainage for eight days, which diminished gradually. After the first few days the patient steadily improved; he was discharged twenty-two days after the operation. He made a complete recovery and is now enjoying excellent health.

CASE 3.—The third patient was a woman, aged 32, who became ill five days before admission to the hospital. She had severe pain in the upper left quadrant, nausea and vomiting, and on entrance to the hospital was profoundly shocked, mentally confused and cyanotic. Her general condition was so grave that it seemed practically useless to submit her to an operation.

When the abdomen was opened, a large amount of serosanguineous fluid was present in the peritoneal cavity, with numerous areas of fat necrosis. The

lesser peritoneal cavity was filled with a heavy exudate, and the gastrocolic and gastrohepatic omentums were apparently on the verge of necrosis. No associated biliary lesions were found.

Drainage of the lesser cavity was established through the gastrohepatic omentum; while the posterior surface of the pancreas was being drained, the finger was introduced into the lesser peritoneal cavity by breaking through the peritoneum at the upper border of the pancreas.

Drainage was profuse; six days after operation food began to appear in the drainage, and for ten days leakage of food continued, which must have been due to sloughing of the posterior wall of the stomach. This patient made a slow recovery and was in the hospital forty-three days.

She reported to me about two months ago, in good physical condition, and stated that she "felt as well as she ever did."

CASE 4.—The fourth patient was a man, aged 40, who had been ill five days with acute pain in the upper part of the abdomen, which was not relieved by morphine. He had had a similar attack two months before presentation, which lasted two days. On admission to the hospital he was acutely ill, with moderate cyanosis and a rapid and thready pulse.

Laparotomy was immediately performed. A large amount of chocolate-colored fluid was found in the peritoneal cavity. The pancreas was swollen and discolored, with many hemorrhagic areas over the entire gland. The wall of the gallbladder was thickened, contracted and adherent to the omentum. When the gallbladder was opened, a thick, dark bile and numerous small stones were found.

The pancreas was drained from its posterior surface, and the lesser peritoneal cavity was drained by breaking through the peritoneum at the upper border of the pancreas. The gallbladder was also drained.

The pancreatic drainage was almost unbelievably profuse and showed little sign of diminishing until the third week. The patient made a satisfactory recovery after remaining in the hospital forty days.

He reported two years later; his general health was good, except for occasional attacks of moderate pain in the right hypochondriac region and tenderness in the region of the gallbladder.

CASE 5.—The fifth patient was a man, aged 50, who entered the hospital because of intense pain in the upper part of the abdomen, which began eight days before entrance to the hospital, but which had greatly increased in severity during the last seventeen hours before admittance. This patient had marked arteriosclerosis; the blood pressure was 180 systolic and 102 diastolic. There was marked tenderness in the entire right side of the abdomen, and rigidity was pronounced.

An immediate exploratory laparotomy was performed. The abdomen contained approximately a pint of a serosanguineous fluid. There was a widespread peppering of fat necrosis. The pancreas was enlarged and boggy, and was hemorrhagic throughout. There was also a postperitoneal ecchymosis along the cecum. No associated biliary lesion could be made out. The pancreas was drained by the method to be described.

There was profuse drainage in this case, and the patient made satisfactory improvement until the ninth postoperative day, when the incision opened and was immediately closed. The patient had an uneventful convalescence, and was discharged from the hospital twenty-seven days after admission.

Case 6.—The sixth patient was a man, aged 50, who for several years had had periodic attacks of severe pain in the region of the gallbladder, with nausea and vomiting. The last attack occurred one month before admission to the hospital. His present illness began one day before admission with excruciating pain in the upper right quadrant, which was only partly relieved by repeated hypodermic injections of morphine. The patient had paraplegia of the lower extremities, which had been present since an injury to the spine in 1907.

On admission the patient was in visible distress, with pain and tenderness of the upper right quadrant and to a lesser degree of the upper left quadrant.

When the abdomen was opened, a large amount of serous fluid was found free in the abdominal cavity. The pancreas was enlarged and more firm than usual. There were a number of old, firm adhesions about the gallbladder. No gallstones were found.

The pancreas was drained by the method to be described.

He made an uneventful recovery and remained in the hospital for twenty-three days. This case was referred to me, but in my absence the operation was performed by Dr. H. E. Sloan and my associate, Dr. C. C. Greer, both of whom were familiar with the method of drainage described. Although neither of them had performed drainage by this method before, they stated that it was easily and quickly done.

After failure in my first case, when the surgical risk was apparently good, and when I had carefully followed out the well recognized transgastrocolic route of drainage with a battery of tubes and later drainage of the gallbladder, and then had lost the patient from what I believed to be inadequate drainage, I made a careful study of the anatomy in the region of the pancreas from textbooks, Edinburgh stereoscopic anatomy and cadaver, and decided that drainage from the posterior surface could be more easily and adequately obtained than from the superior or inferior surface.

With this in view I worked out the following method, which is decidedly difficult to describe and illustrate, but which is simple and easy to perform.

In this series not one case was positively diagnosed before operation, and in only three cases was pancreatitis suspected.

The symptoms usually suggested an acute pathologic condition of the upper right quadrant of the abdomen, and a right rectus incision was made in every case.

OPERATION FOR DRAINAGE FROM THE POSTERIOR SURFACE OF THE PANCREAS

A liberal right rectus incision is preferred. Before drainage is established, associated lesions should be located, and the peritoneal toilet completed. The pancreas is easily exposed by lifting the transverse colon and omentum. It is easily recognized by the characteristic pinkish color, if normal, or by the pathologic changes, if acutely diseased. The head of the pancreas rests in the curve of the duodenum (fig. 1).
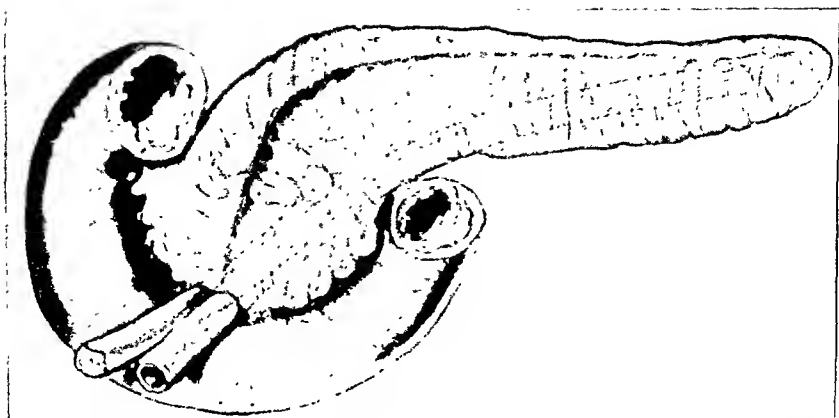
Fig. 1.—The location of the drainage tubes with relation to the pancreas and the duodenum.
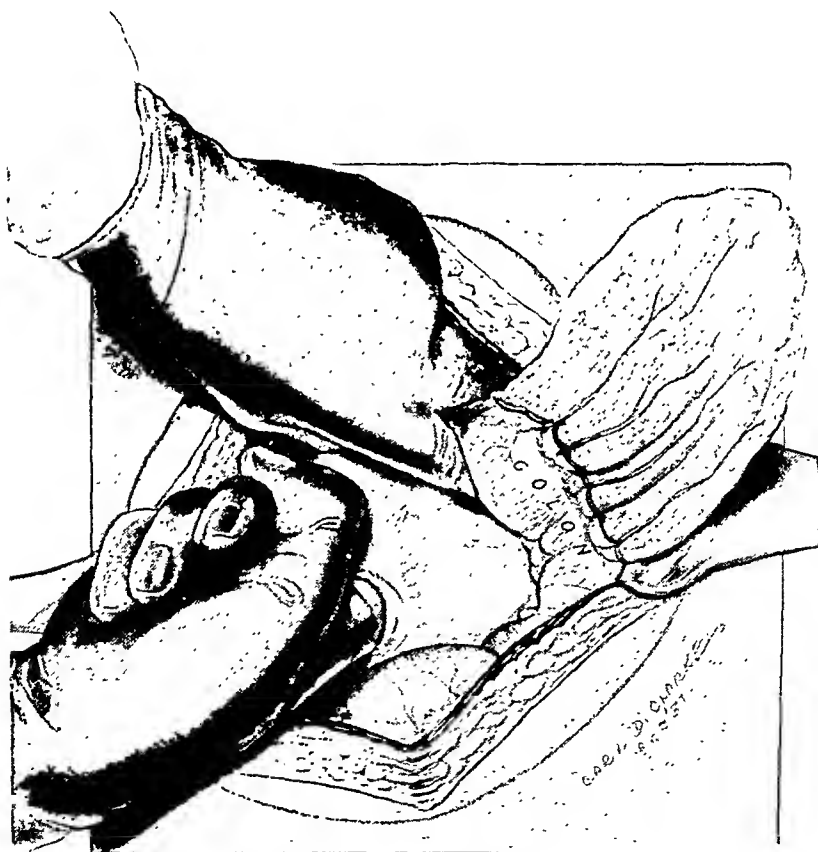
Fig. 2.—The right index finger is shown freeing the posterior surface of the pancreas, preparatory to drainage, with left middle and index fingers on anterior and inferior surfaces acting as guide.

On the lower portion of the head, a little to the mesial side, there is usually a small area of peritoneum which is practically free from blood vessels. At this point the peritoneum is incised, and a blunt hemostat or dissecting scissors is introduced, and the dissection is carried down under the peritoneum to the line of cleavage between the pancreas and the duodenum. The line of cleavage is opened carefully in order not to wound the duodenum or pancreaticoduodenal vessels.

After this space has been opened sufficiently to admit the index finger, the remainder of the dissection is made entirely with the finger, and the pancreas is raised out of its normal position. With the index and middle finger of the left hand as a guide (fig. 2), it is easy to open the space immediately behind the head, body and tail of the pancreas or any part of it that the operator may
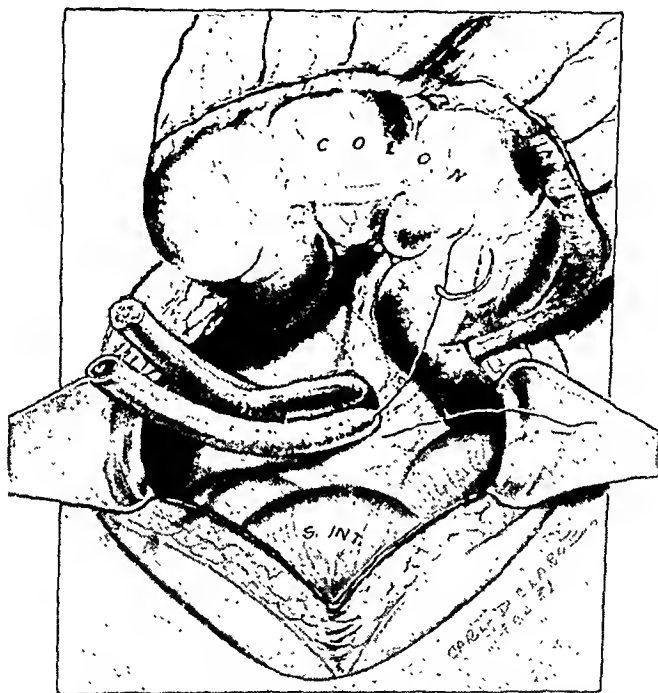
Fig. 3.—The method of draining the pancreas, showing the tube anchored to the peritoneum with no. 0 plain catgut suture.

desire. If there is a sufficient amount of inflammatory product in the lesser peritoneal cavity to necessitate drainage, it can be easily established by breaking through the peritoneum at the upper border of the pancreas. This is easily done with the finger, because bringing the pancreas forward puts the peritoneum at this point on tension. The opening is in the posterior wall of the lesser peritoneal cavity.

In two of the foregoing cases I did this and placed a drain directly into the lesser peritoneal cavity.

When making this dissection with the finger, it must be remembered that there are many important structures in this region. The most important of these are the portal vein, superior mesenteric artery and vein, pancreaticoduodenal vessels and duodenum. A safe rule is to keep the dissecting finger as close to
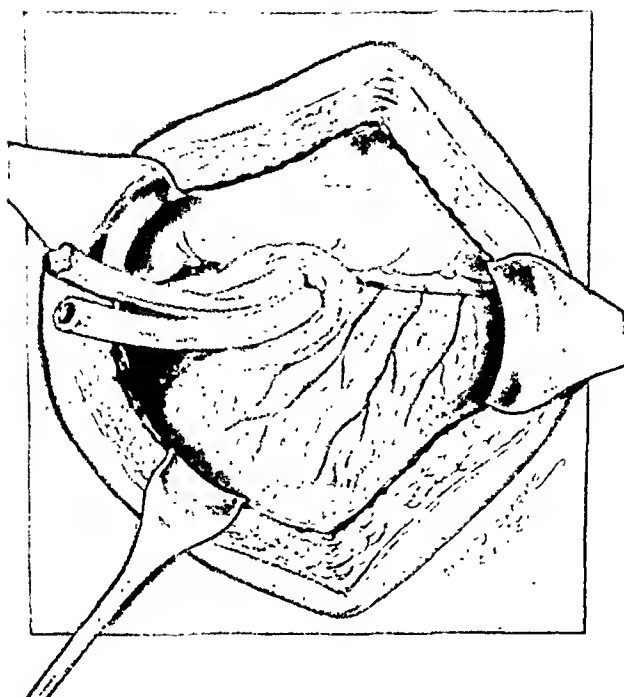
Fig. 4.—The transverse colon brought into normal position, and the omentum draped around the drainage tubes.
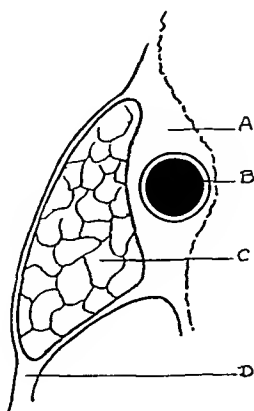
Fig. 5.—Schematic drawing of the tube drain along the posterior surface. *A* indicates retropancreatic space produced by dissection with finger; *B*, drainage tube; *C*, pancreas, and *D*, transverse mesocolon.

the posterior surface of the pancreas as possible, keeping the pancreas between the index and middle fingers of the opposite hand and bringing the pancreas forward carefully, avoiding any unnecessary disturbance of the retroperitoneal tissues.

This space should be opened thoroughly behind all the areas that are thought to be inflamed; if in doubt as to how much to open, it is better to open too much than too little; this space may be drained equally well by different methods.

The method I have used is to place a good-sized tube drain along the posterior surface, as shown in figure 1 and in the schematic drawing, figure 5, and a cigaret or Penrose tubing directly behind the head of the pancreas (fig. 1). The tube is anchored to the peritoneum with no. 0 plain catgut suture, as shown in figure 3.

The transverse colon is brought down to its normal position, and the omentum is draped carefully around the drainage tubes (fig. 4).

In closing the abdominal wall, the drainage tubes are brought out at an easy curve to prevent kinking.

Drainage following the operation varies with the severity of the case. When the drainage is profuse, after the third day I introduce a catheter through the drainage tube and irrigate with a nonirritating, sterile solution. After the fifth or sixth day the tube is removed, and irrigation is made through the sinus tract. After cleansing and sterilization, the tube is replaced.

None of the five cases drained from the posterior surface, as described, has presented any symptoms that could be attributed to lack of drainage. If drainage is the chief object of the operation, it seems that this method has decided advantages over any other method that I have been able to find. In no case has it been necessary to clamp or ligate any bleeding points about the pancreas.

The following are all the methods found in my limited library and in a review of the literature: transgastrocolic omental route, transgastrohepatic omental route, infracolic omental route, drainage through foramen of Winslow and loin drainage.

None of these methods furnish adequate drainage to the retroperitoneal space.

The main advantage of the procedure here described is that it affords:

1. Better opportunity to palpate the gland, thereby yielding a much better conception of the pathologic changes and points where drainage is most essential.

2. Better drainage (more dependent drainage).

3. Less hemorrhage.

4. Fewer postoperative adhesions.

5. Easier performance.

In my opinion this method of drainage, in the hands of competent surgeons, will materially reduce the mortality from acute pancreatitis.

MADURA FOOT

A THIRD CASE OF MONOSPOROSIS IN A NATIVE AMERICAN

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In some countries the deep mycoses are called surgical mycoses. Presenting, as they do at times, a surgical problem, the report of a case of Madura foot seems appropriate, as the surgeon is most likely to see such conditions in the initial stages of the disease when the diagnosis is most difficult.

The term "Madura foot" was coined by the natives of India to designate a deformity of the foot most commonly seen in the vicinity of Madura, a town situated in the southern part of Deccan, at the foot of the Eastern Ghats. When Vandyke Carter,[1] in 1860, established the fungous nature of the condition, he introduced the term "mycetoma"—tumor due to a fungus. This prominent English author in later years recognized the close resemblance of the condition to actinomycosis. During the following decades, a number of widely different fungi were thought to be the cause of mycetoma, and the subject of Madura foot became more and more confused because there was not a clear conception of the term. After the preliminary work of Brumpt[2] and Pinoy,[3] Chalmers and Archibald,[4] in 1916, gave a definition that permits a more exact differentiation from allied conditions.

1. Carter, Henry Vandyke: Tr. M. & Phys. Soc. 6:104, 1860, quoted by Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, ed. 3, New York, William Wood & Company, 1919.

2. Brumpt, E.: Les Mycétomes, Arch. de parasitol. 10:489, 1906.

3. Pinoy, E.: Actinomycoses et Mycétomes, Bull. Inst. Pasteur 11:929 and 977, 1913.

4. Chalmers, A. J., and Archibald, R. G.: A Sudanese Maduromycosis, Ann. Trop. Med. 10:169 (Sept.) 1916.

We do not wish to go too much into detail, as one of us [5] in recent years reviewed this subject elsewhere. It will be sufficient to state, then, that a mycetoma is a growth or granuloma characterized by sinus formation. White, yellow, black or red granules made up of fungous elements are found either in the discharge or embedded in the pathologic tissue.

The presence of definite granules differentiates the mycetomas from other mycoses such as pseudomycetomas and paramycetomas. Chalmers and Archibald [4] subdivided the mycetomas into: (1) actinomycoses, or those forms of mycetoma with granules composed of fine nonsegmented mycelial filaments in which usually the walls are not clearly defined from the contents and in which chlamydospores are absent, and (2) maduromycoses, or those forms of mycetoma with grains composed of large segmented mycelial filaments possessing well defined walls, and usually chlamydospores.

It is obvious that the actinomycotic type of mycetoma is nothing but an actinomycosis of the foot and should not be separated from the actinomycoses in general. It is equally obvious that maduromycoses may occur in any part of the body, just as the actinomycoses do.

As knowledge of the etiology and experimental pathology of mycetoma is in a state of constant evolution, it is not astonishing that this classification already has become somewhat obsolete. There are actinomycoses known in which grains ("sulphur granules") are absent. In fact, it is doubtful whether one is justified in still making the presence of grains composed of fungous elements the criterion by which one differentiates the deep mycoses, since Tarozzi and Barbanti [6] demonstrated that it is possible to produce experimentally the picture of mycetoma with one of the best known surface parasites, Achorion schoenleinii. In keeping with the etiologic classification of diseases in other fields of medicine, the mycologic standpoint seems the only logical one. But most fungi found in mycetoma are fungi imperfecti or hyphomycetes, the botanic position of which is rather problematic and by no means final. Therefore, the classification of Chalmers and Archibald [4] still gives the clinician a satisfactory lead in solving his mycologic problems and in classifying the mycoses.

It is evident from the preceding paragraphs that Madura foot is merely a clinical term and synonym for mycetoma of the foot. It does not imply any information as to the etiology, except as to the fungous

5. Gammel, John A.: The Etiology of Maduromycosis: With a Mycologic Report on Two New Species Observed in the United States, Arch. Dermat. & Syph. **15**:241 (March) 1927; Der Madurafuss, Zentralbl. f. Haut- u. Geschlechtskr. **29:** 393, 1929.

6. Tarozzi, G., and Barbanti, R.: Actinomicosi e Monosporosi, Atti. d. r. Accad. di sc. lett. ed arti, Modena. sez. sc., s. 3a **12:**321, 1916.

origin and the presence of granules. The maduromycoses or "true mycetomas" (Pinoy, 1913) are of greater interest than the actinomycoses on account of the variety of fungi found in this type of mycetoma. Yet the clinical and pathologic pictures produced by these organisms, belonging to three different classes of the vegetable kingdom, are quite uniform. Ten genera harbor fungi described as causes of maduromycosis: Madurella, Indiella, Glenospora, Monosporium, Torula, Allescheria, Aspergillus, Sterigmatocystis, Penicillium and Mucor. All of these molds have one common feature: In their defense against unfavorable conditions in the host or in culture they are able to form granules of various sizes, shapes and colors. These granules are composed of hyphae, spores and usually chlamydospores and are easily visible to the naked eye.

TABLE 1.—*Maduromycoses in the United States*

Author	State	Locali- zation	Color of Grains	Causative Fungus	Where Reported
J. H. Wright............	Mass.	Foot	Black	Unknown	Tr. A. Am. Phys. **13**: 471, 1898
Boyd and Crutchfield..	Texas	Foot	White	Allescheria boydii	Am. J. Trop. Med. **1**: 215 (July) 1921
Gammel, Miskdjian and Thatcher	Ohio	Foot	Black	Madurella americana	Arch. Dermat. & Syph. **13**: 66 (Jan.) 1926
Thompson and Ikeda..	Minn.	Foot	Black	Madurella Ikedai	Arch. Surg. **16**: 764, (March) 1928
C. R. Halloran.........	N. Y.	Foot	Melanoid	Unknown	Arch. Dermat. & Syph. **16**: 611 (Nov.) 1927
Puestow..............	Wis.	Neck	Black	Aspergillus nidulans	Arch. Dermat. & Syph. **20**: 642 (Nov.) 1929
Gay and Bigelow......	Mass.	Foot	White	Monosporium apiospermum	Am. J. Path. **6**: 325 (May) 1930
Jones and Alden.......	Ga.	Foot	White	Monosporium apiospermum	J. A. M. A. **96**: 256 (Jan. 24) 1931

It is somewhat difficult to analyze the literature on mycetoma or Madura foot observed in the United States, because the mycologic data in some of the earlier reports are inadequate. For the sake of brevity and convenience, we have tabulated those cases in which we were reasonably sure that the condition was maduromycoses. Either thick septate hyphae have been described or black granules were seen, for proved cases of actinomycoses with black grains have hitherto been unknown.

The tabulation shows, contrary to expectation, that in a tropical or subtropical disease the majority of the reports originate from the northern part of the United States, but on closer analysis it is found that most patients originally came from the South. Wright's patient might have acquired the infection in Italy; only Puestow's patient had never been south prior to the onset of the illness. The fact that all but one case have been reported during the past decade is due to

increased interest and more widespread knowledge of the disease rather than to an actual increase in the number. The last two cases reported from this country were due to Monosporium apiospermum. We shall report a third case caused by the same organism.

REPORT OF A CASE

History.—G. R., born in 1875, a colored laborer, gave a history of having had a genital sore in 1895 and smallpox in 1906. Since 1910, he had had three separate injuries to the right foot while living on a farm in Virginia, from each of which he seemed to have recovered without any visible change in the condition of the affected part.

In 1917, the right foot was crushed by a wagon in a street of Baltimore and rather severely injured. The patient thought that since that time the ankle and foot had remained swollen and tender, but though he limped, he was able to do heavy labor. Two years later, the foot became larger and more painful, and there was a discharge from numerous openings. The patient entered the Baltimore City Hospital and received, aside from local attention, antisyphilitic treatment, though the Wassermann reactions of the blood and spinal fluid were negative. In the same year he spent nine days at the University Hospital. The records (1919) indicate that there was a brawny induration about the ankle and foot on which were several whitish nodular elevations and two sinuses from which came a thin grayish discharge. The roentgen diagnosis was chronic syphilitic osteitis. In spite of the handicap of an enlarging, discharging and painful foot, the patient continued to work until March, 1926, when all of the symptoms became aggravated.

The patient was admitted from the dispensary to the orthopedic service of the University Hospital on Aug. 5, 1926.

Examination.—Physical examination gave negative results, except for the loss of weight and a low grade fever, rarely over 99.6 F. The right foot, the ankle and the lower half of the leg were swollen to about three times the normal size. The swelling was tender and brawny, though in some places it was boggy. Over the entire dorsum of the foot and about the ankle were multiple punched-out, flat-mouthed sinuses, white around the edges, which when probed were found to be fairly deep and from which a thin, grayish, purulent material discharged. No granules were ever seen, though sought for. The longitudinal arch had collapsed, and the foot was markedly abducted. There were no sinuses on the leg. Movements of flexion and extension at the ankle were retained. The toes and heel appeared to be of normal size, and they were not involved.

Laboratory examination showed that the urine was normal. The blood count showed secondary anemia without leukocytosis or eosinophilia. The Wassermann reaction was negative. Cultures from the sinuses produced stapylococci and streptococci but no fungi. A report on the biopsy specimen suggested either syphilis or tuberculosis.

The roentgenograms showed a marked deformity of the entire right foot, with collapse of the bony elements. There was considerable destruction of bone with evidence of bone formation in the nature of productive periostitis of the lower thirds of the shafts of the tibia and fibula. Obliteration of the joints with fusion of the tarsus and metatarsus was demonstrated.
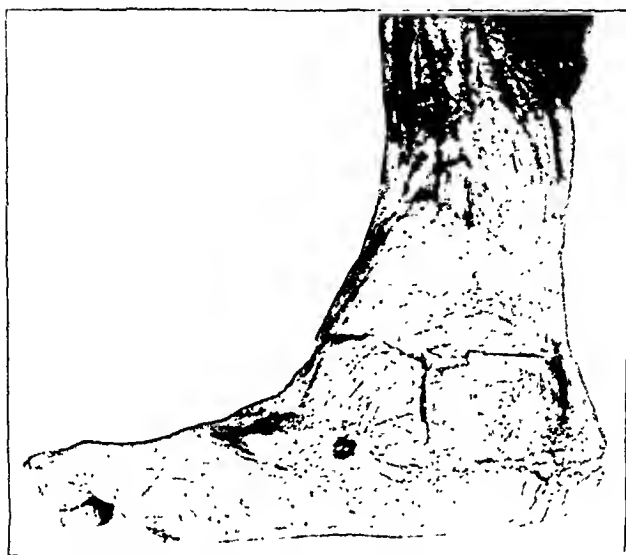
Fig. 1.—Lateral view of the amputated foot.
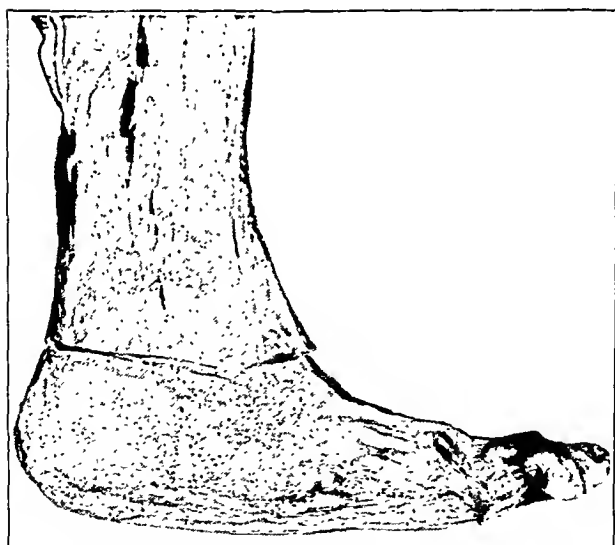
Fig. 2.—Sagittal section of the amputated foot. Part of the osseous structure is destroyed.

While the patient was in the hospital, he was given a prolonged course of potassium iodide in large doses, without improvement. Rest in bed and boric acid dressings were of no avail. The differential diagnosis rested between syphilis, tuberculosis and mycetoma, with the latter predominating, though no "grains" were ever demonstrated, even though they were diligently sought. From the physical and roentgen appearance, it was concluded that destruction and degeneration of the foot and ankle had gone so far that restitution of function was impossible.
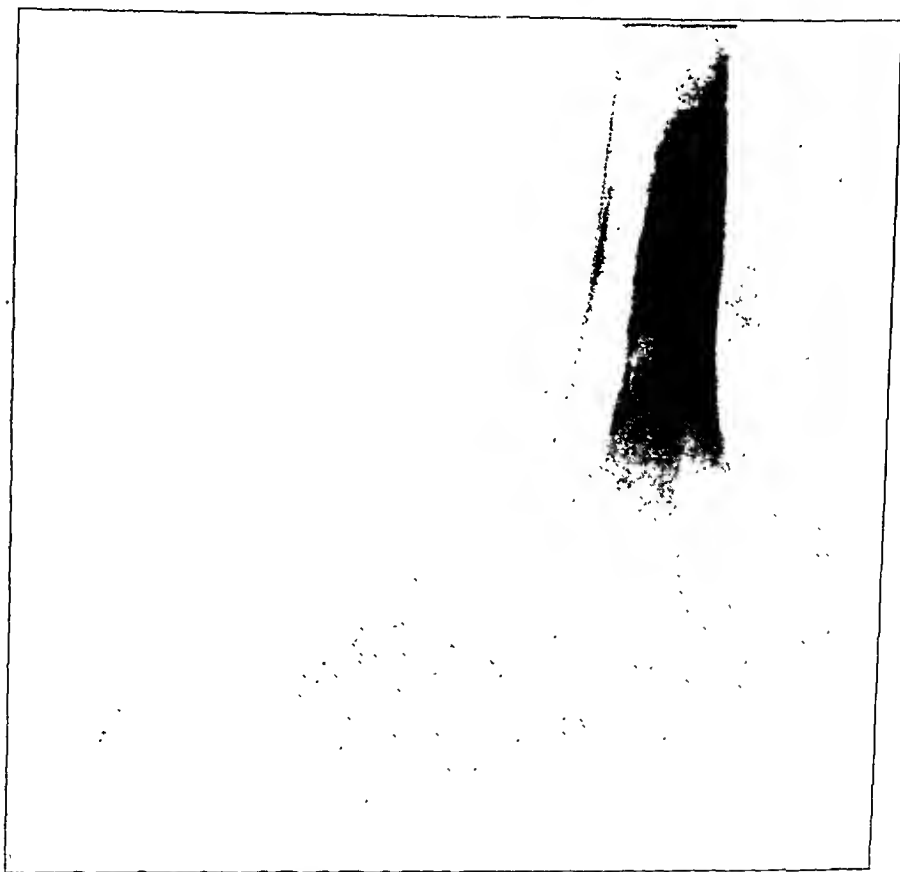
Fig. 3.—Roentgenogram of the right foot, lateral view.

Operation and Course.—Accordingly, on September 11, amputation of the lower part of the right leg about 6 inches (15 cm.) below the knee was performed. The patient made an uneventful recovery. He was discharged on October 13, and later was able to get about fairly well on a home-made "peg-leg."

Subsequent Course.—The patient was seen from time to time. Roentgen examinations of the stump did not reveal recurrence in the bone, and there were no evidences clinically. In May, 1928, a visit to the patient's home disclosed that he had died from "stomach trouble" two weeks previously.

Pathologic Examination.—The foot and leg were swollen and indurated, and there were many sinuses of various sizes opening through the skin. On section the sinus tracts were seen to be of labyrinthine complexity, extending through

the soft tissue and bone and communicating between many tissue spaces, which were filled with thick gray pus. All of the soft tissues as well as bone were involved in this proliferative and degenerative process, and there was marked fibrosis around the necrotic areas. It was only then that, for the first time, grains were found freely in the purulent discharge.

Histologic Examination.—The histologic examination was made by Dr. Alan R. Moritz of Lakeside Hospital. There was extensive destruction and replacement of tissues by a productive inflammatory process, which was characterized by small and large and often confluent, granulomatous lesions. The smaller
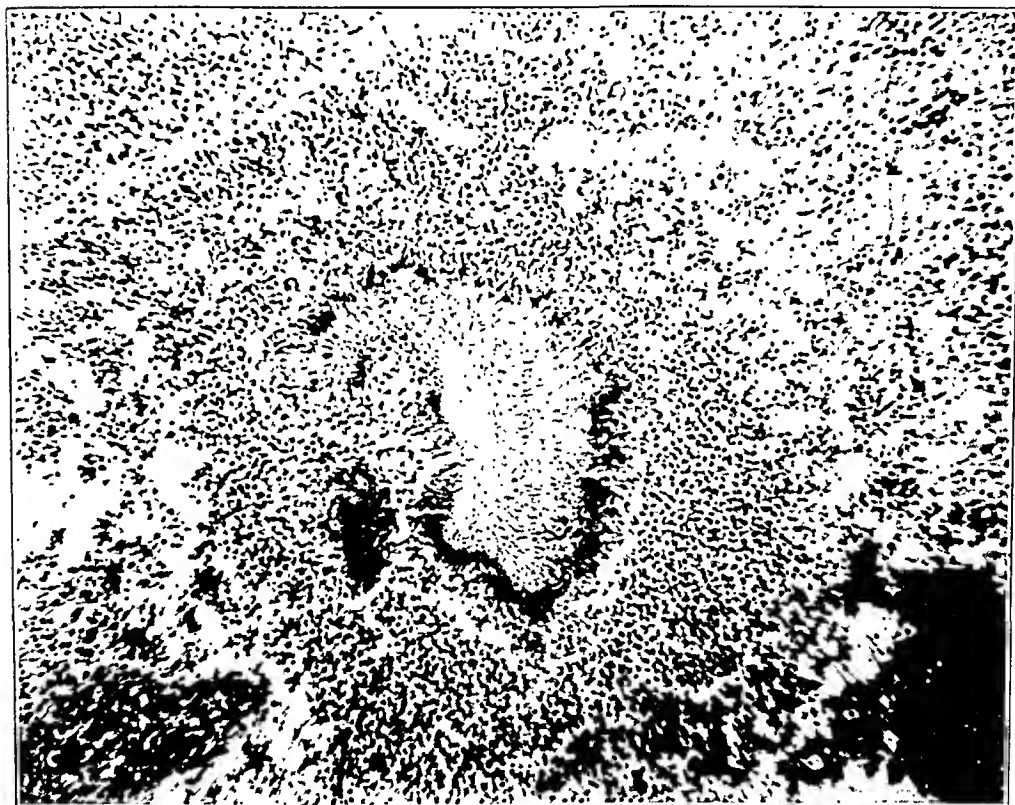
Fig. 4.—Grain in situ.

lesions consisted chiefly of focal collections of thickly disposed macrophages. These cells were round or polyhedral, approximated one another closely and had faintly acidophilic, vesicular cytoplasm. The nuclei were regular, large, round and pale-staining. Around these sharply circumscribed collections of cells there was an exudation of lymphocytes and polymorphonuclear leukocytes. These smaller granulomas were found in tissue interstices, with displacement rather than destruction of adjacent structures. The larger lesions were associated with destruction of the adjacent tissue, and intermingled with the peripheral zone of macrophages were many granulocytes, a few of which were eosinophilic. Giant cells of the foreign body type were numerous. Central necrosis was common, and the necrosis in some lesions was coagulative and in some liquefactive. The

necrotic central zones in many places were undergoing organization by polypoid masses of richly vascularized granulation tissue. Fibroblastic proliferation with resulting dense cicatrization was widespread.

In several of the granulomas, large (up to 1 mm.), irregularly outlined acidophilic granules were present. From the surfaces of these granules projected regularly disposed radial filaments, some of which were clubbed at the ends. The main body of some of the granules was comprised entirely of what appeared to be a tangled mass of acidophilic mycelium, while in others there were many
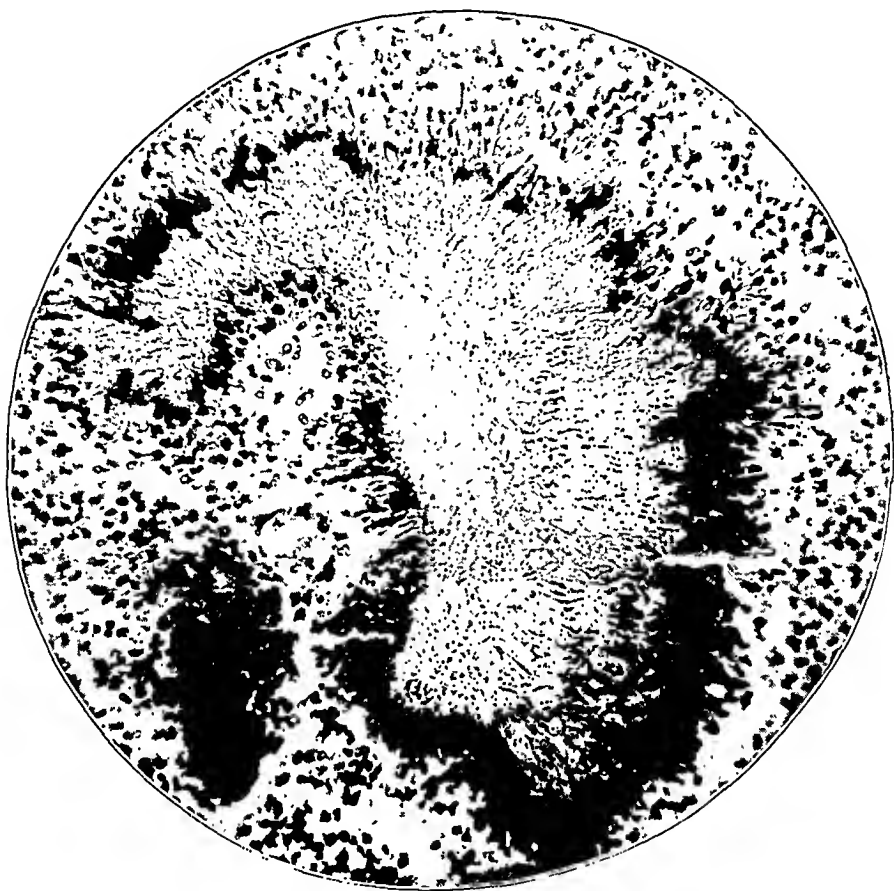
Fig. 5.—Grain in situ.

small round or ovoid, unstained, light brown spores. The spores measured about 12 microns in diameter and showed peripheral condensation. They were not confined to the granules, but were scattered diffusely, though not in large numbers, through the granulation tissue and in the central necrotic zones. Occasionally they were seen within small giant cells.

The status of mycetoma, especially the clinical side, was discussed by Thompson [7] in 1928. The case here reported is typical in all respects:

7. Thompson, H. L.: Present Status of Mycetoma, Arch. Surg. **16**:774 (March) 1928.

the history of trauma, the slow onset without a definite period of incubation, the relatively small discomfort during the first few years, the failure of iodine therapy, so efficient in some of the other mycoses, and the uncontrollable progress, necessitating eventual amputation. The rather monotonous, clinical and pathologic picture is contrasted with the multiplicity of causative organisms. Therefore the mycologic part of this study seemed to us most attractive.

When the foot was amputated in 1926, some of the granules found in the abscesses in the depth of the tissues were planted on various mediums, and the growth of a white mold was easily obtained. The thick septate mycelium established the diagnosis of maduromycosis, but an identification of the fungus was not attempted. Four years later, from 1930 to 1931, mycologic and experimental studies were carried out in the laboratories of Western Reserve University, subcultures from the original growth being used.
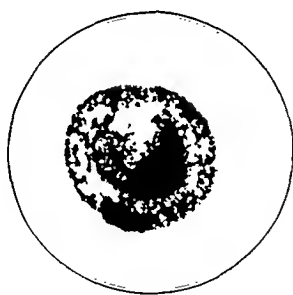
Fig. 6.—Colony of Monosporium apiospermum. One week's growth on Sabouraud's dextrose agar at room temperature.

MYCOLOGY

The fungus grows well on the usual mediums for molds. A few days after the inoculation, a snowy white tuft of fine mycelial filaments appears on the surface of the medium and spreads peripherally. On Sabouraud's dextrose or maltose agar the colonies reach a diameter of from 1.5 to 2.2 cm. after one week and about 6 cm. after three weeks' incubation at room temperature. There is marked retardation of growth in the incubator. A full-grown culture usually shows a central knob or an elevation with radiating furrows. Concentric rings in the mycelium are sometimes seen. A constant feature is a black base from which delicate, grayish, cottony, densely interwoven hyphae rise to about from 3 to 4 mm. above the surface. The growth does not push farther than from 2 to 3 mm. below the surface of the substratum. The black color of the base is due to the darkening of the spores. There does not seem to be diffusion of the pigment into the medium. On the surface of solid mediums the formation of pinhead-sized black granules

(sclerotes) is occasionally observed. Sections stained with hematoxylin and eosin fail to demonstrate any perithecia.

The modus of reproduction was studied in hanging drop cultures with Sabouraud's dextrose peptone broth, a modified Sabouraud's technic being employed. The central part of the mycelium is closely intertwined; the peripheral hyphae are hyaline and septate and branch rarely. Their diameter varies between 2.4 and 3 microns. The hyphae or lateral conidiophores, which in turn may branch again, usually terminate in a single piriform or ovoid spore from 8 to 12 microns in length and from 4 to 5.5 microns in width. Here and there, one coni-
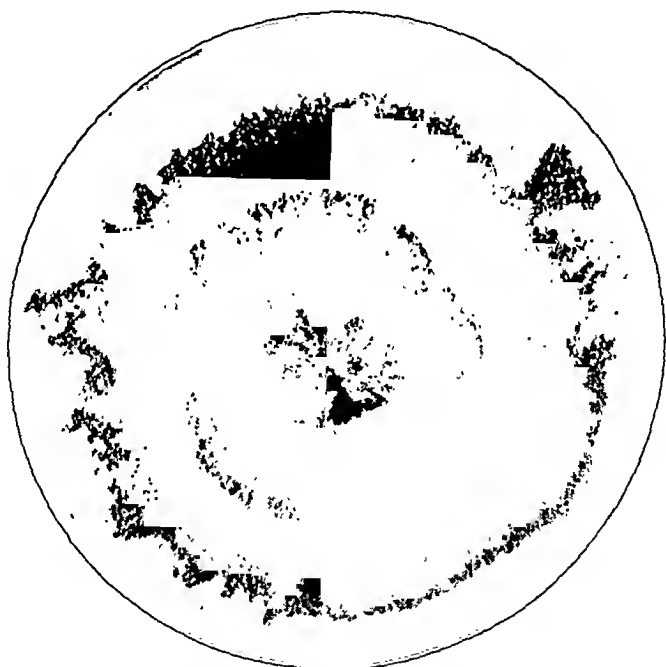
Fig. 7.—Monosporium apiospermum. Four weeks' growth at room temperature.

diophore seems to give rise to two or three conidia. The protoplasm of the mycelial segments and spores shows everywhere small granules or droplets. Young spores are hyaline; old ones are brown. Chlamydospores are rarely seen and then only in old cultures. Gelatinized human serum is not liquefied; gelatin shows liquefaction.

The cultural and morphologic characters clearly classify the fungus as a hyphomycete belonging to the order Conidiosporales, suborder Sporophorineae. Our observations correspond in the essential features with Saccardo's [8] description of Monosporium apiospermum. Compar-

8. Saccardo, P. A.: Sylloge fungorum omnium hucusque cognitorum, 1911, vol. 22, p. 1287. Information through courtesy of Dr. John H. Barnhart, New York Botanical Garden.

ing the mycologic data in the literature on the various strains, we found considerable variations in the descriptions, which, however, prominent mycologists consider as being within physiologic limits. We hesitated at first to identify the fungus in question as Monosporium apiospermum because sometimes more than one spore is born on a conidiophore, but we found that this deviation from the original description has been
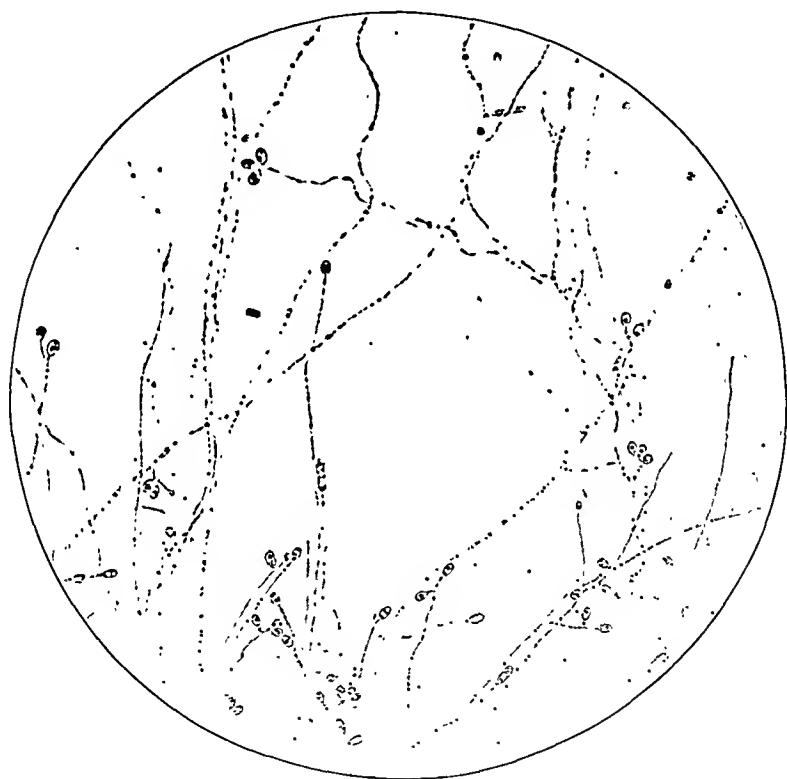
Fig. 8.—Hanging drop culture of Monosporium apiospermum.

observed by other investigators,[9] too, and Prof. Gino Pollacci [10] of the University of Padua concurred in our diagnosis.

Monosporium apiospermum, Saccardo [8] (1911) is found in the literature also as Scedosporium apiospermum (Saccardo, 1911) and as Aleurisma apiospermum (Saccardo), (Maire, 1921 [9]). It is considered by many to be identical with Scedosporium sclerotiale (seu nigricans,

9. Montpellier, J., and Gouillon: Mycétome du pied (type pied de Madura) dû à l'Aleurisma apiospermum, Bull. Soc. path. exot. 14:285, 1921.

10. Polacci, Gino, and Nannizzi Arturo. I miceti patogeni dell'uomo e degli animali, Siena, Stab. Arti Grafiche S. Bernardino, 1923, pt. 2.

Pepere, 1914 [11]). Table 2 shows that it has been found in Europe, Africa and both Americas. It has been observed as the cause of maduromycosis more frequently than any other organism. Unfortunately, our studies, too, have failed to reveal the complete life cycle of the organism or its host.

ANIMAL EXPERIMENTATION

Suspensions of spores and hyphae from cultures were injected into the knee joints of two rabbits. After two weeks a swelling developed in both animals at the site of injection, which gradually enlarged. One animal died after two months with a tremendous swelling of the knee;

TABLE 2.—*Madura Foot Due to Monosporium Apiospermum*

Author	Country	Animal Experiments	Where Reported
Tarozzi	Italy	Positive	Atti d. Soc. ital. di. patol., set. 1909
Radaeli	Italy	Positive	Sperimentale, Arch. di biol. 65 : 383, 1911
Pepere	Italy	Positive	Sperimentale, Arch. di biol. (suppl.) 67 : 213, 1913; 68 : 531, 1914
de Magalhães	Brazil	None	Ann. da policlin. geraldo, Rio de Janeiro, Dec., 1916
Linhares	Brazil	None	Thèse de Rio de Janeiro, 1917
Montpellier and Gouillon	Algeria	None	Bull. Soc. path. exot. 14 : 285, 1921
Montpellier	Algeria	None	Bull. Soc. path. exot. 17 : 755, 1924
Anderson	Algeria	None	Arch. Inst. Pasteur de Tunis 14 : 90, 1925
Fonseca and Area Leao	Brazil	None	Compt. rend. Soc. de biol. 97 : 1847, 1927
Delamare and Gatti*	Paraguay	None	Compt. rend. Acad. d. sc. 188 : 1264, 1931
Gay and Bigelow	U. S.	Negative	Am. J. Path. 6 : 325 (May) 1930
Jones and Alden	U. S.	Negative	J. A. M. A. 96 : 256 (Jan. 24) 1931

* This organism was originally described as Indiella americana but was later identified by Paul Peña as Monosporium apiospermum (Compt. rend. Soc. de biol. 104 : 689, 1930).

crepitus could be felt easily. Unfortunately, the animal was disposed of by the attendant before autopsy could be performed. At the same time, the other animal seemed to show some improvement, there being less swelling and local heat. It was killed on the seventieth day. There were several walled-off abscesses around the knee. The synovial fluid was increased and slightly purulent. Retrocultures from bits of muscles, from the abscesses and the articular fluid gave positive results. A detailed study of the mechanism of the infection in a larger series of animals will be published later.

11. Pepere, A.: Micetoma a grani neri del piede, Sperimentale, Arch. di biol. (suppl.) **67**:213, 1913; Sul funge parasita di un micetoma a grani neri del piede (Carter) nostrana [Monosporium apiospermum, Sacc., (M. sclerotiale)] Sperimentale, Arch. di biol. **68**:531, 1914.

SUMMARY

A third case of monosporosis under the clinical picture of Madura foot of the white grain variety occurring in a native American is reported.

Mycetomas due to higher fungi rarely respond to medical treatment (iodides and compound tincture of iodine given intravenously, etc.) ; therefore they belong to the domain of surgery.

In cases of chronic osteomyelitis and tuberculosis or syphilis of the bone, the possibility of a mycosis should be considered.

Monosporium apiospermum injected into the knee joints of rabbits results in a purulent arthritis with periarthritic abscesses from which retrocultures are positive. This is the first instance in which experiments on animals carried out with a fungus isolated from a patient with maduromycosis in the United States yielded positive results.

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VASOCONSTRICTOR FIBERS

PERIPHERAL COURSE AS REVEALED BY A ROENTGENOGRAPHIC METHOD

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In view of the persisting difference in opinion among surgeons as to the efficacy of "periarterial sympathectomy" as compared to sympathetic gangliectomy, a further study of the peripheral course of the vasoconstrictor neurons has recently been made. By means of a modification of Brooks' sodium iodide technic for the roentgenographic visualization of the femoral arterial tree, quite definite results have been obtained in the laboratory animal, which seem to constitute convincing evidence as to the location of the peripheral vasconstrictor pathways to the lower extremity.

METHOD

Brooks,[1] in 1924, demonstrated the possibility of roentgenographic visualization of the femoral arterial tree in man by means of the injection of a concentrated solution of sodium iodide. In the experiments to be reported Brooks' method has been modified only in that the iodide has been injected into the abdominal aorta, with the result that both femoral trees have been visualized at the same moment. By comparing the caliber of the larger arteries in the two limbs and the degree of filling of the smaller vessels, it has been possible to judge quite satisfactorily the degree of vascular constriction in either limb relative to the other.

Adult male cats were used in these studies. Under ether or sodium amytal anesthesia a laparotomy was done, and the abdominal aorta and inferior vena cava were isolated below the renal vessels. A temporary arterial clip was applied to both cava and aorta at this level, and from 1.5 to 2 cc. of 100 per cent sodium iodide was injected into the aorta below the clip and with the needle directed toward the aortic bifurcation.

1. Brooks, B.: Intra-Arterial Injection of Sodium Iodid, J. A. M. A. **82:** 1016 (March 29) 1924.

Immediately following the injection, one or more roentgenographic pictures of the hind quarters were taken with the operator holding the extremities in positions as nearly symmetrical as possible. The clips were then removed from aorta and vein, allowing resumption of femoral circulations. The entrance into the general circulation of the quantity of sodium iodide required for good visualization of both femoral trees was always followed by death within a few hours.

With occasional exceptions, this method has given a surprisingly good portrayal of the arteries of the lower extremities (fig. 1). The method is of advantage because it is objective, permitting comparison as to symmetry of caliber and of filling of identical vessels in the two limbs, photographed at the same instant under one filling-pressure. The method thus becomes useful in determining the presence or absence of unilateral changes in arterial caliber following any procedure whatsoever.

The disadvantages of the method are several. Although the sodium salt is the least toxic of the more soluble inorganic iodides, a quantity sufficient for satisfactory delineation of the vessels of both hind limbs of the cat invariably proves lethal when, the picture having been taken, the clip is removed from the cava and the iodide allowed to enter the general circulation. Therefore only one determination can be made in each animal. Furthermore, the method is limited in that it does not reveal the absolute degree of constriction or dilatation in a given artery but only its caliber relative to that of the corresponding vessel of the opposite limb.

The roentgenogram must be taken as soon as possible after the iodide is injected. Otherwise the picture shows a blurring of the intervascular spaces. There are two possible explanations of this phenomenon. One is that the shadow is due to the entrance of iodide into vessels too small for individual visualization but which in their aggregate cause a partial opacity. On the other hand, it may be that the iodide diffuses through the walls of the vessels to cause a shadow in extravascular areas. Obviously, such diffusion could not occur in so short a time from the large thick-walled arteries; its occurrence would denote the presence of the iodide in thin-walled vessels. A vasodilatation lowers resistance to flow and would favor the entrance of the solution into the smaller radicles. Therefore, whether the shadow in question is due to the presence of iodide in microscopic vessels or to its diffusion from them, the shadow will appear at an earlier moment in limbs where the arterial system is dilated. Figure 1 is a print from a roentgenogram taken approximately ten seconds after sodium iodide was injected into the abdominal aorta of a normal

cat. Figure 2, picturing conditions in the same animal from twenty-five to thirty seconds after the same injection, demonstrates this blurring and loss of contrast.

The 100 per cent sodium iodide solution is evidently quite irritating. Normal animals anesthetized to a sufficient degree to submit quietly
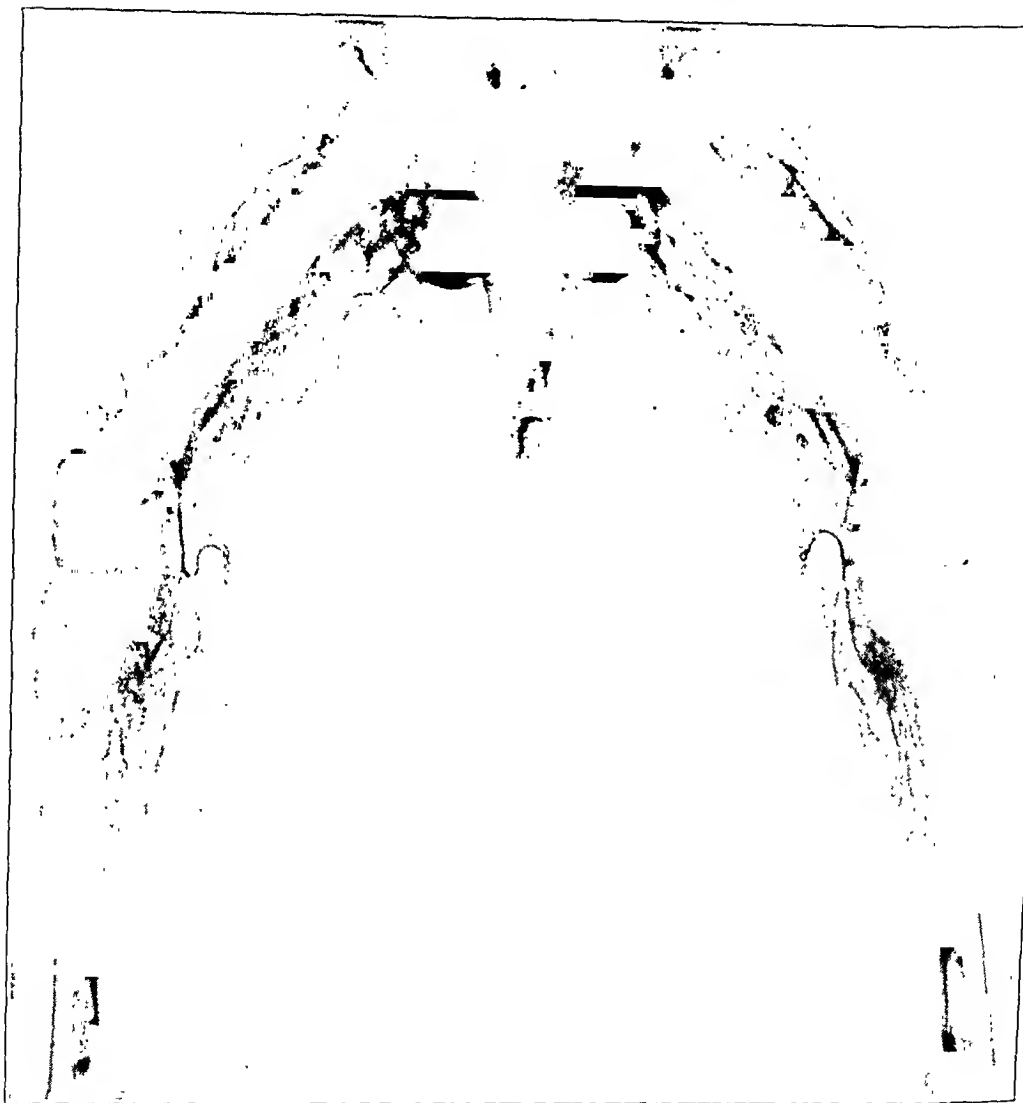
Fig. 1.—Arterial systems of lower extremities of the living cat, as shown by a roentgenogram taken ten seconds after the injection of concentrated solution of sodium iodide into the abdominal aorta.

to laparotomy invariably stir and cry out as the solution is injected into the vessels. Since a similar injection of physiologic solution of sodium chloride induces no such reaction, it must be the nature of the solution and not distention of the vessel that causes the outcry when the iodide is injected.

RESULTS

Arterial Caliber Following Sympathetic Gangliectomy.—In a number of animals a determination was made of the effect on arterial caliber of the removal of one lumbar sympathetic chain. In the cat there are five or more lumbar sympathetic ganglions. These ganglions, with the
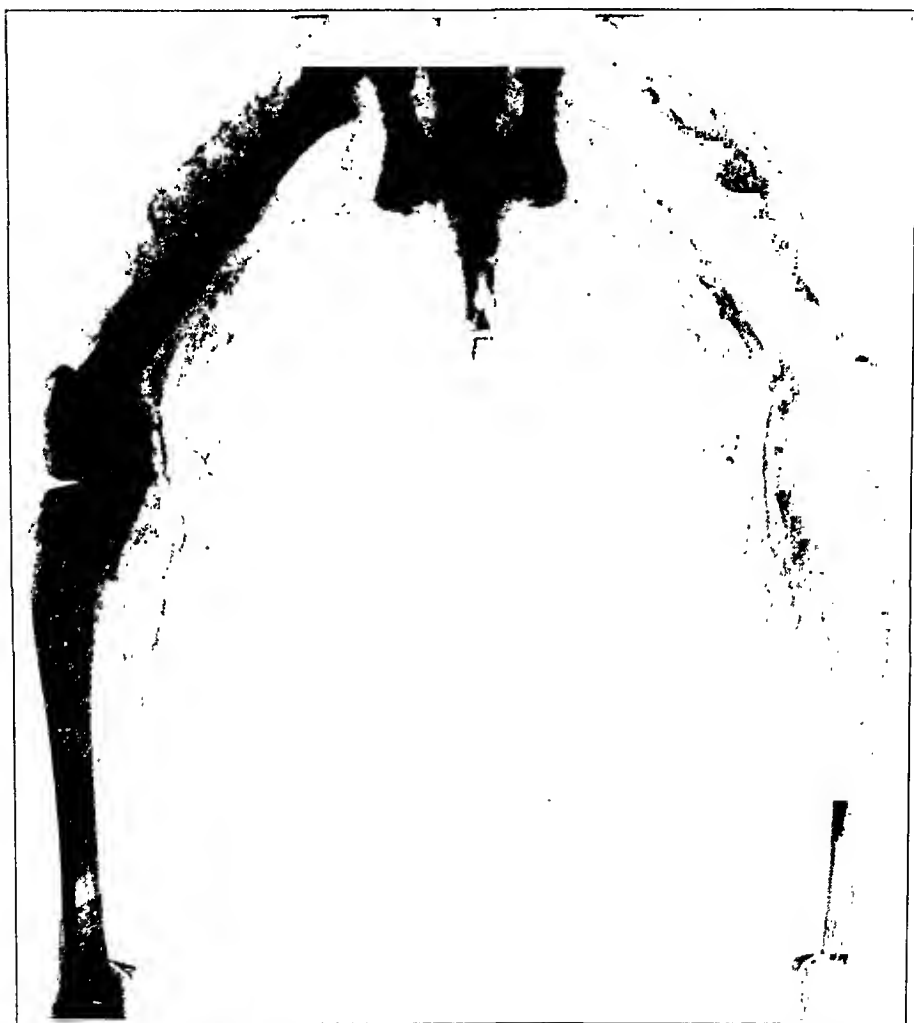
Fig. 2.—Roentgenogram of the same animal, taken fifteen seconds after figure 1. In the interim the iodide had become so distributed as to cause a blurring of the intervascular spaces.

intervening strands of fibers, were removed on one side. In order to prevent the confusing effects of reflex secretion of epinephrine, the adrenal gland of the same side was denervated by section of the major splanchnic nerve and the opposite adrenal was excised. At varying

intervals after the sympathectomy an injection of sodium iodide was given and a roentgenogram taken.

Figure 3 is a print from a roentgenogram of both legs taken immediately after resection of the left lumbar sympathetic ganglions. One sees a much greater filling of vessels on the left than on the right,
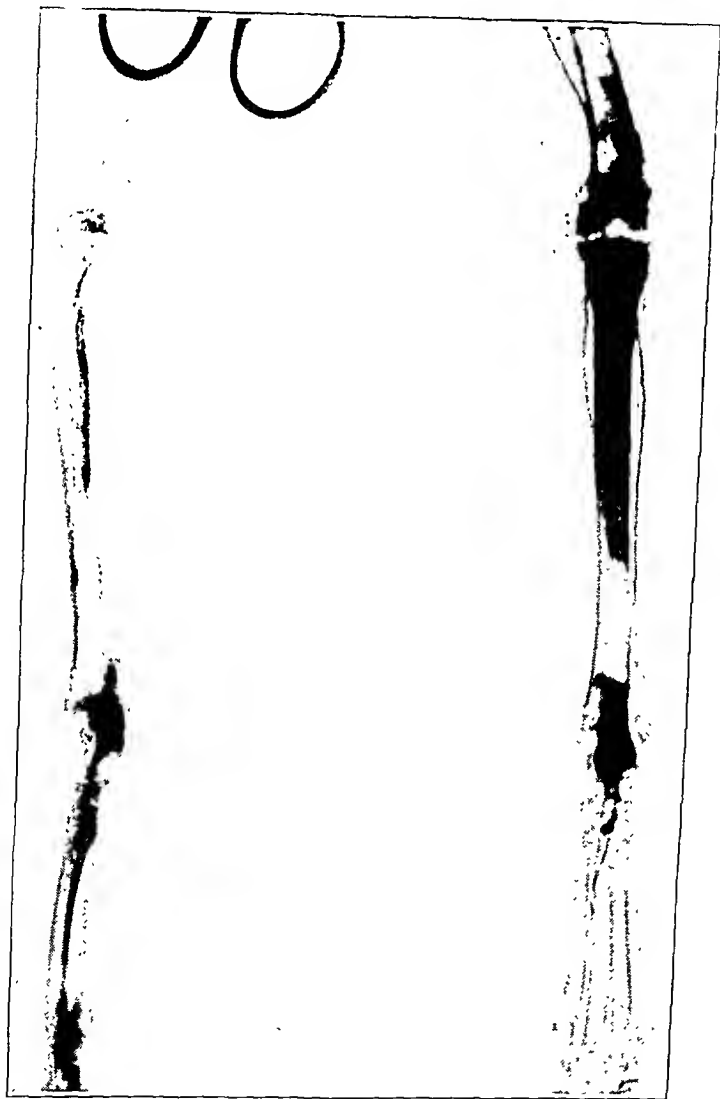
Fig. 3.—Roentgenogram of a living cat taken following the injection of iodide into the abdominal aorta immediately after left lumbar sympathectomy. The arteries of the left lower extremity are dilated relative to those of the right.

indicating a marked vasodilatation following sympathetic gangliectomy. Figure 4 shows a pronounced vasodilatation throughout the entire left extremity in an animal subjected to left lumbar sympathectomy *ten weeks* prior to the taking of the picture. Therefore, the vasodilatation

following sympathetic gangliectomy is not a temporary phenomenon. Figure 5 was taken more than seven weeks after a lumbar sympathectomy. After the injection was made there was a delay before the roentgenogram was taken. One sees a blurring throughout the entire sympathectomized extremity. Obviously, much more iodide was present
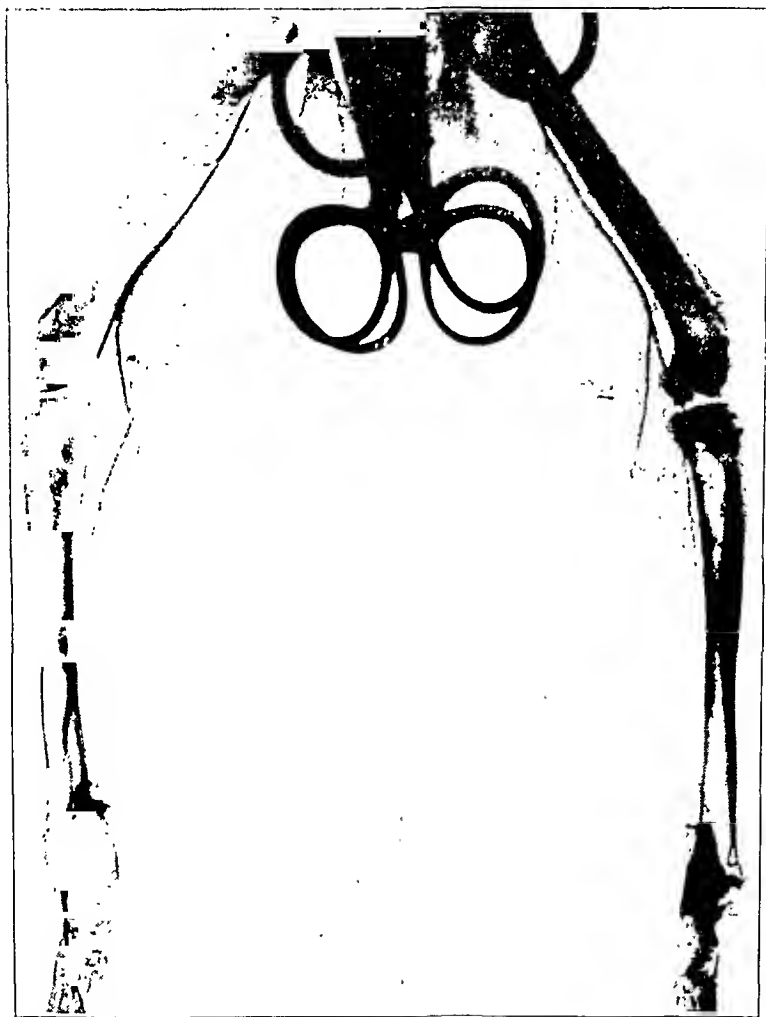
Fig. 4.—Roentgenogram following injection made ten weeks after left lumbar sympathectomy. The arteries of the left extremity are still dilated.

than was in the opposite limb. There is not a good delineation of vessels. The blurring, which regularly occurs if too much time elapses between injection and picture, must denote, as stated, the presence of iodide in microscopic radicles. or its diffusion from them. In this animal (fig. 5). the blurring is much more marked on the sympa-

thectomized side, indicating a more rapid passage of the solution into the finer vessels on that side, and thus implying a loss of vasoconstriction following sympathectomy.

In the final animal of this series there was a definite increase in vascular caliber eleven weeks after sympathectomy. In our experience,
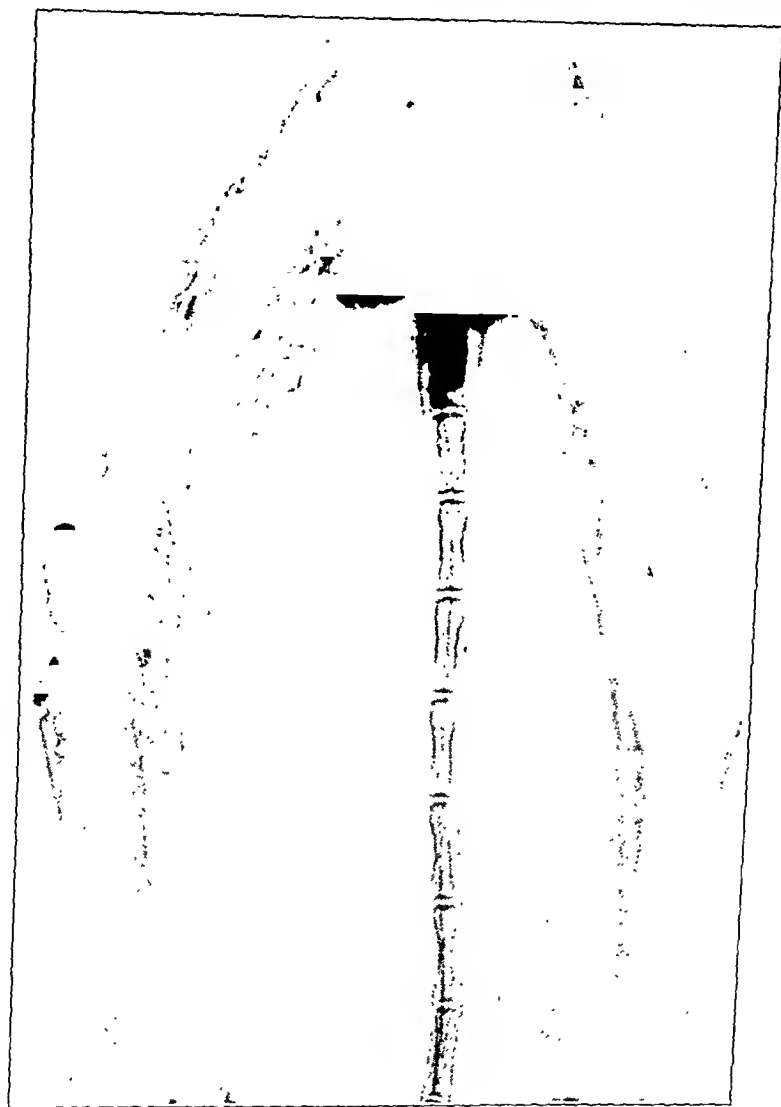
Fig. 5.—Roentgenogram following injection made seven weeks after left lumbar sympathectomy. The arteries of the left lower extremity are dilated (see text).

sympathetic gangliectomy has always produced a vasodilatation, which has been demonstrable by the sodium iodide method.

Arterial Caliber Following the Section of Somatic Nerve Trunks.— Injections and pictures were made at varying periods of time following

the section of one or another of the peripheral nerve trunks distal to the rami communicantes. Figures 6 and 7 illustrate a result that has been of constant occurrence after section of the sciatic trunk just external to the greater sciatic foramen. One sees throughout the entire extremity, though most marked in the lateral region of the thigh, a pronounced
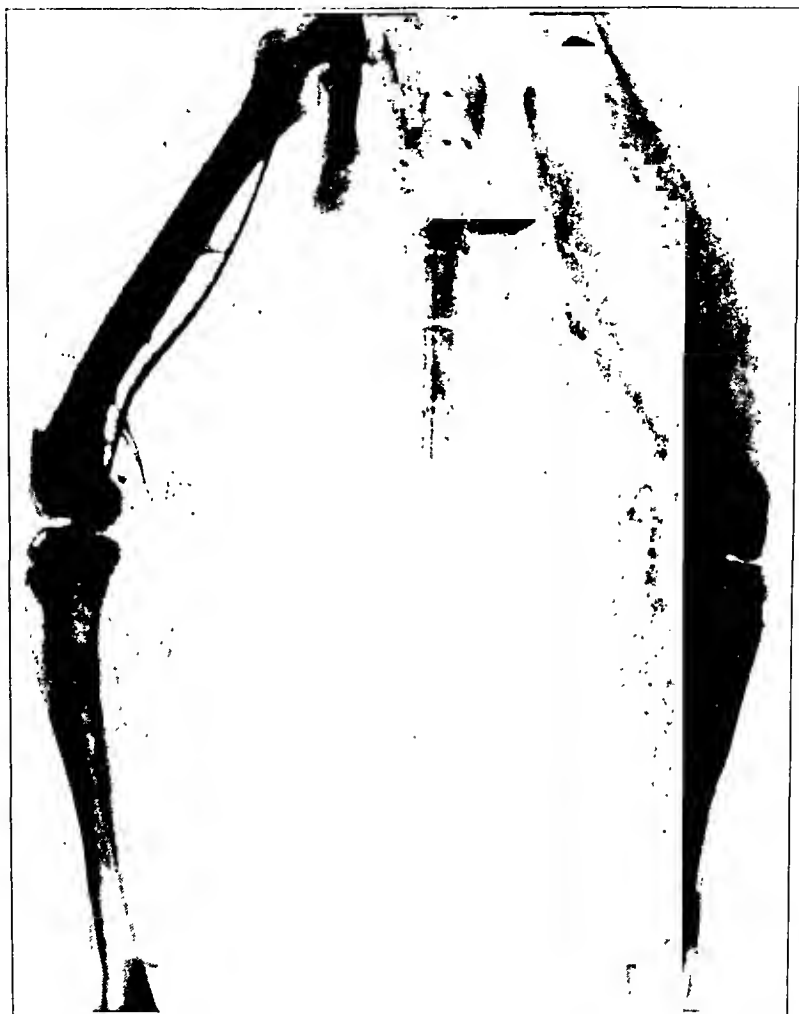
Fig. 6.—Roentgenogram showing vasodilatation in the left lower extremity following section of the left sciatic nerve.

increase in intervascular opacity as compared with the opposite limb. The area of increased opacity does not coincide with the site of the operative wound, but extends throughout the entire extremity. It is not a result of the paralysis of skeletal muscles, for it is most marked in the regions of the gluteal muscles and of the vastus lateralis, and

these muscles are not innervated by the sciatic nerve. As stated before, it must be due to the presence of the iodide in microscopic vessels or to its diffusion through their walls into extravascular areas. It seems reasonable, therefore, to consider this opacity an evidence of a vasodilatation that has permitted the iodide to enter the lumina of
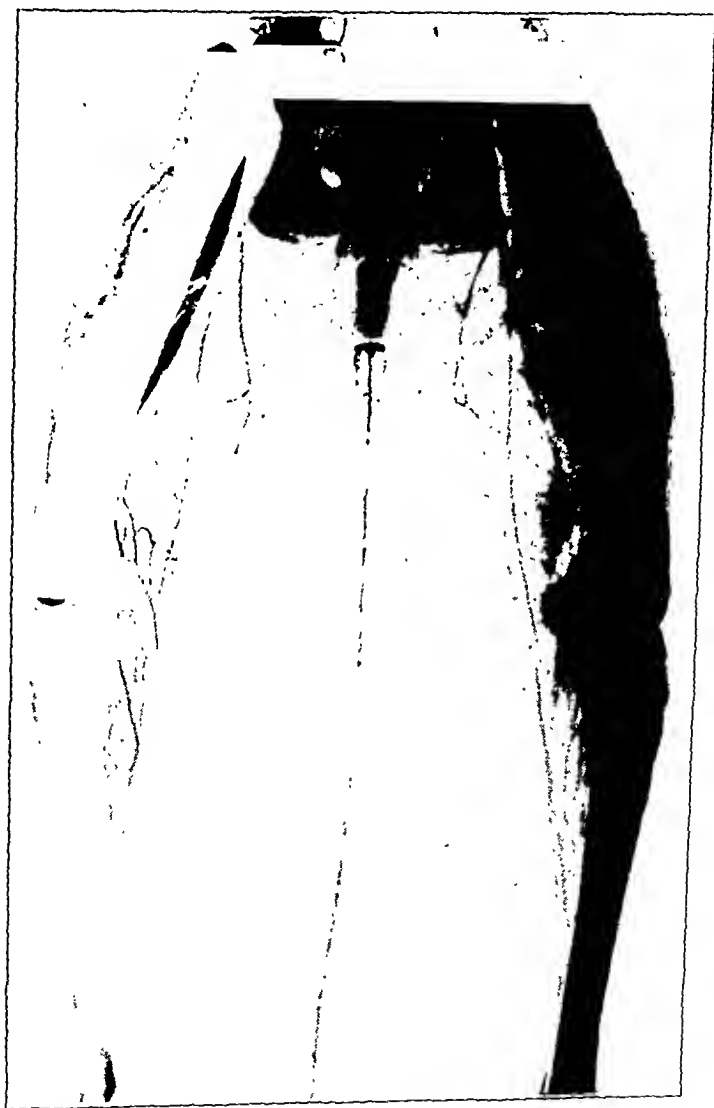
Fig. 7.—Roentgenogram showing pronounced vasodilatation in the lateral region of the left thigh following section of the left sciatic nerve.

microscopic vessels at a more rapid rate in the limb operated on than in the contralateral normal limb. The constancy of this finding has led to the conclusion that vasoconstrictor fibers are present in the sciatic nerve at the level of the sciatic foramen.

In cat 60 the femoral nerve was severed just peripheral to the inguinal ligament. Figure 8 shows the extreme unilateral dilatation of the vessels below the site of this section. Obviously, vasoconstrictor fibers were present in large number. However, this finding has been inconstant, occurring in about 50 per cent of the cases. Perhaps, since
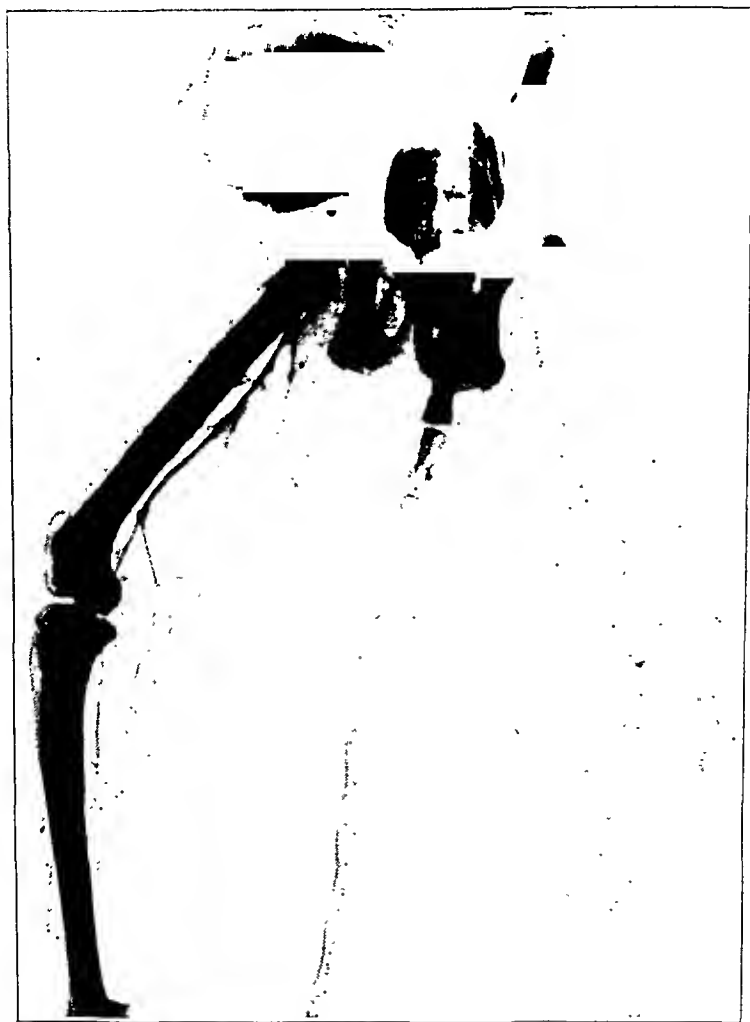
Fig. 8.—Roentgenogram showing dilatation of the right femoral arterial tree following section of the right femoral nerve.

the sciatic nerve also contains vasoconstrictor fibers, in certain instances the sciatic fibers alone may suffice to maintain vascular symmetry. Moreover, the method in use does not reveal the absolute caliber of the arteries but only the caliber relative to that of the vessels of the

opposite limb. Therefore, in those instances in which section of the
femoral nerve did not result in vascular asymmetry, it is quite possible
that some disturbing factor, e. g., profound anesthesia, so depressed
vasoconstrictor activity throughout the entire system that section of
vasoconstrictor neurons had no further effect on the size of the vessels.

Fig. 9.—Roentgenogram taken four days after right femoral "periarterial sym-
pathectomy." No significant vasodilatation followed the operation.

Arterial Caliber Following "Periarterial Sympathectomy."—The
femoral nerve of the cat lies in contact with the femoral artery. This
fact forbids the use of phenol or other chemical agents as a means of
detecting the presence of vasoconstrictor fibers in the periarterial region.
Periarterial operations have been, therefore, mechanical, and have

included, in addition to a careful stripping of the arterial adventitia, the transverse section of all tissues of the femoral sheath except the trunk artery, the trunk vein and the femoral nerve.

In no case in our experience has this periarterial operation resulted in a vasodilatation. Figures 9, 10 and 11, showing the absence of

Fig. 10.—Roentgenogram taken fifteen days after right femoral "periarterial sympathectomy." No significant vasodilatation had occurred.

dilatation after four, fifteen and twenty-seven days, respectively, are representative of the series. In some cases (figs. 9 and 10) there is a slight constriction on the side operated on. (This constriction may possibly point to the presence of vasodilator fibers in the arterial sheath.) But in no instance has the periarterial operation resulted in a vasodila-

tation that could be demonstrated by this method. This series of experiments included the most satisfactory roentgenographic pictures of the entire study, and the consistently negative results would seem to be reliable proof that no great number of the vasoconstrictor fibers for the lower extremity course distally along the femoral artery.
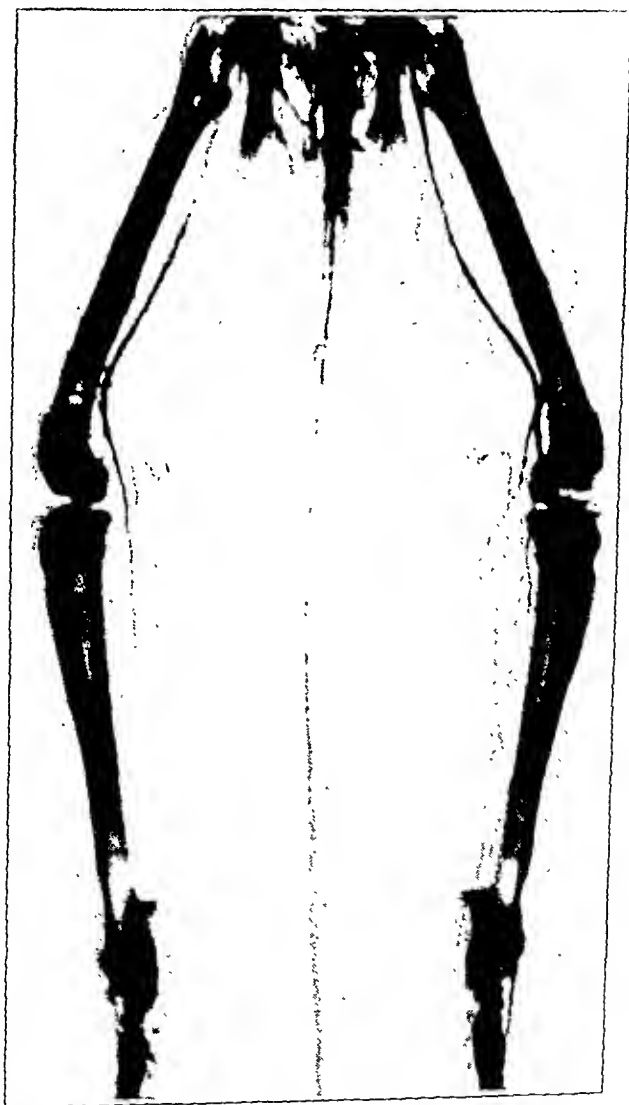
Fig. 11.—Roentgenogram showing absence of dilatation twenty-seven days after right femoral "periarterial sympathectomy."

COMMENT

It has been maintained by some, mainly on the basis of clinical changes observed following "periarterial sympathectomy," that vasoconstrictor fibers, derived supposedly from the sympathetic trunk or from the aortic plexus, extend distally along the femoral artery to play

an important part in the innervation of its smaller branches. Most anatomic findings have been to the contrary. In addition to the older writing in anatomy, recent studies by Potts [2] and by Hirsch [3] in the laboratory animal and by Blair, Duff and Bingham [4] in man have resulted in the repeated demonstration of vasoconstrictor fibers joining the peripheral arteries at irregular intervals after having been conveyed distally in the somatic nerves. Furthermore, these workers were unable to find vasoconstrictor fibers following the femoral artery for any great distance.

The roentgenographic method described in this report has revealed a pronounced vasodilatation following sympathetic gangliectomy. Although varying degrees of dilatation have occurred following the section of sciatic or femoral nerve trunks, in no instance has the periarterial operation produced any degree of dilatation demonstrable by this method. These results serve to confirm those of the authors cited, to the effect that the vasoconstrictor fibers reach the peripheral arteries by way of the somatic nerve branchings.

The literature includes at least one other attempt to study vasomotor function by a roentgenographic method. In 1930, Horton and Craig [5] reported the results of a study of arterial caliber in the lower extremities after sympathetic gangliectomy and after "periarterial sympathectomy" by means of roentgenograms taken following the injection of metallic mercury into the arteries. As the pictures were taken after death, the results cannot be interpreted in terms of nervous activity, and therefore throw no light on the issue in question.

SUMMARY

After ligation of the abdominal aorta above its bifurcation and the injection of a concentrated solution of sodium iodide just distal to the ligature, it is possible to obtain good roentgenographic portrayal of the femoral arterial systems of the living cat (fig. 1). When both lower extremities are included on one film, it is possible to compare as to symmetry of caliber and of filling the corresponding vessels of the two extremities, photographed at the same instant under one injection

2. Potts, L. W.: The Distribution of Nerves to the Arteries of the Leg, Anat. Anz. **47**:138, 1915.

3. Hirsch, L.: Ueber die Nervenversorgung der Gefässe in Hinblick auf die Probleme der periarteriellen Sympathektomie, Arch. f. klin. Chir. **137**:281, 1925.

4. Blair, D. M.; Duff, D., and Bingham, J. A.: The Anatomical Result of Peri-Arterial Sympathectomy, Brit. J. Surg. **18**:215, 1930.

5. Horton, B. T., and Craig, W. McK.: Evidence Shown in Roentgenograms of Changes in the Vascular Tree Following Experimental Sympathetic Gangliectomy, Arch. Surg. **21**:698 (Oct.) 1930.

pressure. The method thus becomes of use in determining the presence or absence of unilateral changes in arterial caliber following any desired procedure.

With this method, one can demonstrate a pronounced increase in the caliber of the arteries after sympathetic gangliectomy (fig. 3). This dilatation following resection of the proper segments of the lumbar sympathetic chain has been found persisting in animals photographed ten and eleven weeks after sympathectomy (fig. 4). No determinations have been made after longer intervals.

Section of the sciatic nerve just distal to its entrance into the extremity regularly causes a widespread vasodilatation, particularly marked in the lateral region of the thigh (figs. 6 and 7).

In approximately half of the cases, section of the femoral nerve at the root of the extremity results in a pronounced increase of the caliber of the entire femoral arterial tree (fig. 8).

In no instance has "periarterial sympathectomy" produced a vasodilatation demonstrable by this method (figs. 9, 10 and 11).

It is concluded that in the cat the constrictor neurons for the femoral arterial system are distributed to the peripheral vessels in fractions by way of the branches of the sciatic and femoral nerve trunks. No appreciable number follow the trunk artery for any considerable distance.

EXPERIMENTAL SURGERY OF THE PULMONIC VALVE

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Two experimental procedures are included in this report: (1) the production of pulmonic stenosis in dogs and (2) the conversion of this lesion into stenosis with insufficiency by partial valvulectomy.

THE PRODUCTION OF PULMONIC STENOSIS

The method was similar to that devised for creating a chronic, sclerosing lesion of the mitral valve, which was reported in a previous paper.[1] Two distinct procedures were carried out: (a) electrocoagulation of the pulmonic valve and (b) intravenous inoculation with cultures of Streptococcus viridans.

(a) *Electrocoagulation of the Pulmonic Valve.*—One-half hour after the administration of morphine hypodermically, the dog was anesthetized with ether, and both sides of the thorax were shaved and cleansed with soap and water. When the animal was fully relaxed, a properly fitting rubber tube was introduced into the larynx through the trachea and attached to a Wolff bottle containing ether, which was, in turn, attached to an Erlanger mechanical respiratory apparatus. The dog was turned on its right side, and the thorax was elevated with a pad. The indifferent electrode of a portable diathermy apparatus producing a bipolar current of high frequency was placed in direct contact with the skin. The operative field was prepared with iodine and alcohol, and the dog and the operating table were draped with sterile linen. An incision was made over the left fifth rib from the angle to the sternum and was carried down through the fascia and muscle to the periosteum. The exposed rib and a portion of the costal cartilage were resected subperiosteally, and the pleura was opened. The lungs were packed off with pads of cotton moistened in warm saline solution. The sterile portion of the active electrode was then attached to the remainder of the apparatus and tested.

1. Powers, J. H.: The Experimental Production of Mitral Stenosis. Arch. Surg. **18**:1945 (April) 1929.

The pericardium was incised medial to and parallel with the left phrenic nerve. The heart was delivered from the pericardial cavity, and a suture was placed in the apex to facilitate subsequent manipulation. A spot for the incision was chosen on the anterior surface of the right ventricle, free from coronary vessels and about 2 cm. below the root of the pulmonic artery. Control sutures were placed on each side of this area; the ends were crossed and held by the assistant. The myocardium was incised, and the insulated electrode was introduced into the cavity of the ventricle. By palpation at the junction of the pulmonic artery and the ventricular wall with the left forefinger and thumb, the operator was able both to feel and to see the location of the tip of the instrument at the pulmonic orifice. When the tip was placed in accurate approximation with the cusps of the valve, the current was applied. When the valve had been traumatized in several areas, the instrument was withdrawn and the wound in the heart was closed with silk sutures. The apex and control sutures were removed, the heart was replaced in the pericardial cavity, and the pericardium was closed with a continuous stitch of fine silk. The cotton pads were removed, the lungs were inflated, and the pleura and thoracic wall were closed in layers. If performed carefully the operation was bloodless throughout.

(*b*) *Intravenous Inoculation with Cultures of Streptococcus Viridans.*—In order to increase the reaction in the traumatized valve, each animal was inoculated twice during the early postoperative course with cultures of Streptococcus viridans. The strain of organisms utilized had been isolated from a case of rheumatic fever. Each animal was given two inoculations of from 30 to 100 cc. of a twenty-four hour broth culture of this organism, usually on the second and fourth postoperative days.

After intervals of three and ten months, two animals were operated on a second time and reinoculated.

Results.—Eight operations were performed on six dogs. The operative mortality was nil. (Similar operations on the mitral valve were followed by an immediate mortality of 22.8 per cent.[1])

Each animal was inoculated with cultures of Streptococcus viridans.

Dog 1.—A systolic murmur developed which disappeared at the end of three months. Secondary coagulation of the pulmonic valve and subsequent inoculations were repeated one month later. After three weeks a systolic murmur developed, and the blood culture was positive for approximately one month from the time of inoculation. During the subsequent five months the animal had a systolic murmur and a systolic thrill, both of which were most pronounced just to the right of the sternum in the third and fourth interspaces. Partial valvulectomy was then performed.

Dog 2.—Immediately after operation both systolic and diastolic murmurs were present. Following inoculations with cultures of Streptococcus viridans and the development of endocarditis, the diastolic murmur disappeared but the systolic murmur persisted. After an interval of two and one-half years examination of the heart disclosed a harsh, roughened first sound and a soft systolic murmur. The animal was killed, and at autopsy the pulmonic cusps were found to be slightly thickened and fibrotic.

Dog 3.—A definite systolic murmur was detected six days after operation. Two and one-half months later the murmur was present but less distinct, and it disappeared entirely in another six weeks. Twenty-seven months later no murmur was present. Postmortem examination of the heart showed two scars in the pulmonic

orifice below the insertion of the cusps which were normal. No stenosis was apparent. When the first operation was performed the tip of the instrument had not been accurately approximated to the cusps of the valve so that only the endocardium at the base of the ventricle had been traumatized.

Dog. 4.—A loud systolic murmur was audible immediately after operation, and was interpreted as due to valvular damage created by the electrocautery. During the stage of acute vegetative endocarditis the murmur was less harsh, but with the
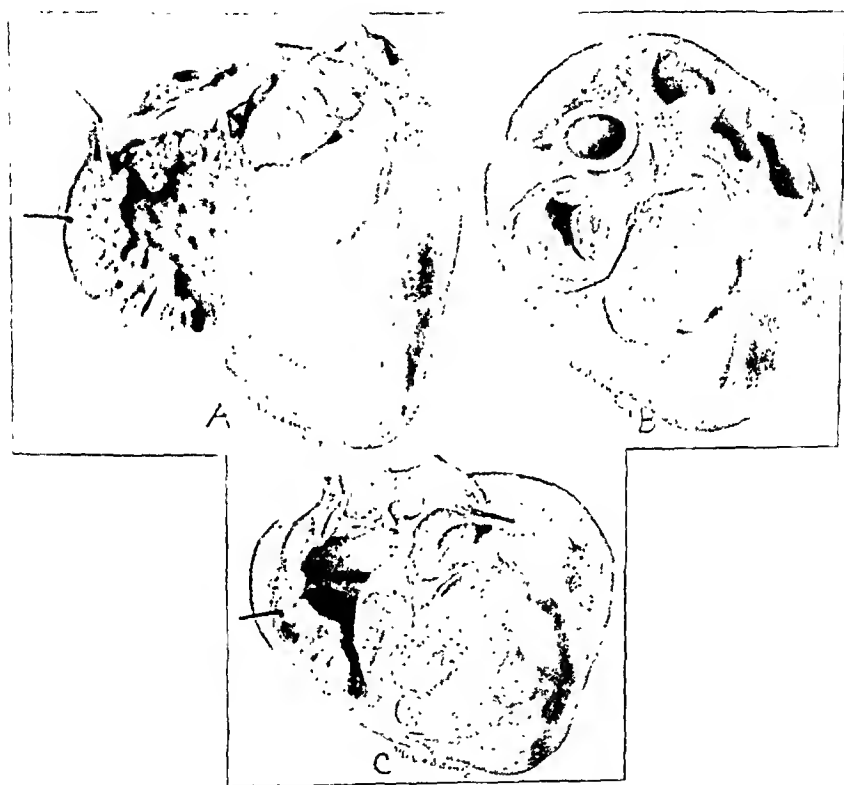
Fig. 1.—A, heart of dog 6. The right ventricle has been opened near the interventricular septum to expose the pulmonic valve with numerous large, warty vegetations attached to the cusps. B, heart of dog 1. The pulmonary artery has been cut away to expose the pulmonic valve from above. The cusps are thickened, fibrous and partially adherent to one another. The defect created by the cardiovalvulotome may be seen in the right posterior cusp. C, heart of dog 4. The right ventricle has been opened to expose the thickened, sclerotic posterior pulmonic cusps. The defect created by the cardiovalvulotome may be seen in the left posterior segment.

development of stenosis, it became loud and blowing. A systolic thrill was present in the pulmonic area. Partial valvulectomy was performed about six months later.

Dog 5.—Two days after the second inoculation with Streptococcus viridans (six days after operation) a soft systolic murmur was audible. A chronic discharging sinus developed at the posterior angle of the wound. The systolic murmur persisted until the animal died three and one-half months later. Autopsy disclosed

a walled-off empyema of the left pleural cavity with which the sinus communicated, diffuse fibrinous pericarditis and vegetative endocarditis of the pulmonic valve. The other cardiac valves were normal.

Dog 6.—Following operation and bacterial inoculation, a systolic murmur developed over the pulmonic area. As the acute vegetative process healed, organisms disappeared from the blood stream. With the development of stenosis, the character of the murmur changed. Three months later a long, blowing murmur was heard throughout systole. As the pulmonic obstruction increased a systolic thrill became palpable.

Secondary coagulation of the valve and reinoculations were carried out in the hope that a more marked stenosis might be produced by further trauma and a superimposed endocarditis. During the postoperative course, a very harsh systolic murmur was heard. The blood culture remained persistently positive. The dog refused food but drank much water, vomited frequently, became lethargic and emaciated, and died on the thirty-seventh day.

Fig. 2.—Roentgenograms showing the heart of dog 1, before and after the development of pulmonic stenosis.

At autopsy the pleural and pericardial cavities were remarkably free from adhesions. There were no pulmonary emboli. The pulmonic orifice was practically occluded by large, warty vegetations adherent to all three cusps (fig. 1, *A*).

Comment.—Electrocoagulation of the pulmonic valve was a less hazardous procedure than a similar operation on the mitral valve, possibly because of the proximity of the auriculoventricular node to the mitral ring. Auricular fibrillation and acute cardiac dilatation, both of which were responsible for immediate fatalities during electrocoagulation of the mitral valve,[1] did not occur in any of these experiments.

During each operation an effort was made to produce as much valvular damage as could be tolerated by the animal. Charring and puckering of the pulmonic cusps were the immediate results of the

procedure. Following intravenous inoculations with cultures of Streptococcus viridans, acute vegetative endocarditis developed on the traumatized valve. Death in one case (dog 6) was due to generalized septicemia and pulmonary occlusion caused by large, warty, fungating vegetations adherent to the margins of the valve. Four of the six animals operated on developed sufficient resistance to overcome the acute infection. As the vegetative process healed, the pulmonic cusps became thickened, fibrous and inelastic. The edges tended to adhere to one another, and chronic stenosis of the orifice was produced (fig. 1, *B*). Clinical evidence in the form of a persistent systolic murmur, accompanied occasionally by a systolic thrill in the pulmonic area, was obtained to support the diagnosis of pulmonic stenosis.

Roentgenograms of the hearts of these animals, taken at a distance of 1 meter with the tube centered over the mid-dorsal spine, showed a progressive increase in the transverse cardiac diameter, apparently due to enlargement of the right side (fig. 2).

Studies of the blood and observations of the red blood cell count, the hemoglobin and the hematocrit value after the development of pulmonic stenosis showed no significant alterations from similar determinations made before operation.

The results may be summarized as follows: One animal died from septicemia and pulmonic occlusion by vegetative thrombi. One animal died because of chronic empyema, pericarditis and acute vegetative endocarditis. In one case, clinical evidence of pulmonic stenosis disappeared at the end of three months and when the animal was killed twenty-seven months later the pulmonic valve was normal. (The tip of the electrode had not been actually approximated to the valve at operation, and consequently the cusps had not been traumatized.) In the remaining three animals clinical and pathologic evidence of pulmonic stenosis developed. Two of them were subsequently operated on again, and the stenosis was converted into stenosis with insufficiency.

None of the valves other than the pulmonary, which had been traumatized by the operative procedure, showed evidence of acute or chronic endocarditis.

CONVERSION OF PULMONIC STENOSIS INTO STENOSIS WITH INSUFFICIENCY BY PARTIAL VALVULECTOMY

Two dogs with well marked stenosis of the pulmonic valve, created by the method already described, were utilized for these experiments. Partial valvulectomy was performed with a cardiovalvulotome [2] similar

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2. Dr. E. C. Cutler contributed this instrument, which was first used in some experimental studies on the surgical treatment of mitral stenosis. Beck, C. S., and Cutler, E. C.: A Cardiovalvulotome, J. Exper. Med. **40**:375 (Sept.) 1924.

to that devised by Beck and Cutler but carrying a shaft of smaller diameter.

Partial Valvulectomy.—The position of the dog on the table and the anesthesia were similar to those employed in the first series of experiments.

The heart was reexposed through the healed scar of the previous incision in the left thoracic wall. Adhesions between the pleura and the lungs or between the lungs and the pericardium were divided by sharp dissection whenever necessary. The pericardium was incised and freed from the anterior wall of the right ventricle where it was adherent at the site of the old myocardial scar. The heart was partially rotated and displaced from its pericardial bed.

Control sutures were placed; the myocardium was incised, and the cardio-valvulotome was introduced into the cavity of the right ventricle. By palpation of the pulmonic ring, at the junction of the heart and pulmonary artery, a scarred segment of the obstructing valve was engaged between the jaws of the instrument, excised and withdrawn from the circulation.

The myocardial wound was sutured, the heart was replaced in the pericardial cavity, and the pericardium, pleura and thoracic wall were closed in layers with silk.

Results.—Partial resection of the stenosed pulmonic valve was well tolerated by each dog.

Dog 1.—This was an animal with experimental pulmonic stenosis produced by the method described in the first half of this paper and recorded in the previous protocols. Partial valvulectomy was performed, and several tiny bits of scarred valve were excised. The systolic thrill disappeared, and a soft diastolic murmur was audible immediately after the operation. The systolic murmur was unchanged. One month later the presence of adventitious sounds in diastole was questionable, but the second sound was indistinct in the pulmonic area. Examination of the heart gave essentially the same results during the following twenty months. The dog was killed at the end of this period. At autopsy multiple adhesions were found between the pleura and the pericardium. (The animal had had three operations on the heart.) There were several dense scars in the pulmonic ring. The cusps of the valve were thickened, fibrous and sclerotic. The edges tended to adhere to one another at the junction of the cusps, and on the posterolateral margin of the valve was seen the defect created by the cardiovalvulotome (fig. 1, *B*).

Dog 4.—This was an animal with experimental pulmonic stenosis and a systolic murmur and thrill in the pulmonic area (see previous protocol). Several attempts with the cardiovalvulotome were made before a scarred segment of the valve was finally engaged between the jaws of the instrument and excised. The systolic thrill largely disappeared, and a questionable diastolic murmur was audible after the operation. Subsequently a long, harsh systolic murmur was always heard but no second sound could be distinguished.

The animal was killed after twenty months. The posterior and lateral cusps of the pulmonic valve were densely scarred and thickened. The anterior cusp was normal. In the posterior segment was found the defect created by the cardio-valvulotome (fig. 1, *C*).

Comment.—Both of these dogs were in good health throughout the postoperative period. No peripheral edema, demonstrable ascites or other evidences of cardiac decompensation were apparent at any time.

These results are in marked contrast to those that followed partial resection of experimental stenosis of the mitral valve in which the immediate mortality was 80 per cent and the final postoperative mortality was 100 per cent.[3]

Because of its comparatively superficial position, the pulmonic valve is relatively accessible to surgical attack. The localization of instruments within the pulmonic orifice may be assisted by both the hand and the eye. With these facts in mind, supported by the increasing tendency of surgery to encroach on the domain of the heart and accompanied by the realization that this organ will tolerate hitherto unsuspected operative manipulation, one may hope that eventually certain selected patients with congenital pulmonic stenosis will be relieved by surgical treatment.

The application of such treatment should be limited to the group of cases described by Abbott in which "the stenosis is usually valvular due to a foetal endocarditis setting in in later embryonic life after the cardiac septa have closed."

The difficulties of making such a clinical diagnosis are great, and the group of cases uncomplicated by other congenital cardiac abnormalities is small. Furthermore, a heart laboring under the embarrassment of an impaired cardiac or circulatory mechanism does not tolerate operative manipulation with the same complaisance as does the normal heart. And lastly, the patient with cardiac disease, either congenital or acquired, will submit to operation only as a last resort. Nevertheless, with improvement in diagnostic facilities and operative technic, surgical invasion of the field of congenital heart disease is not beyond the realm of possibility.

SUMMARY

Electrocoagulation of the pulmonic valve was performed on six dogs and followed by intravenous inoculation with cultures of Streptococcus viridans. Acute vegetative endocarditis developed on the traumatized valve. As these lesions healed, the cusps of the valve became thickened, fibrous and inelastic; the edges tended to adhere to one another, and the end-result was actual stenosis of the pulmonic orifice.

Two of these animals with experimental pulmonic stenosis were subjected to partial resection of the stenosed valve. The operation was well tolerated, and the animals lived for twenty months without evidence of cardiac decompensation.

The suggestion is made that the condition, in certain selected patients with congenital pulmonic stenosis, may be amenable to surgical treatment.

3. Powers, J. H.: The Surgical Treatment of Mitral Stenosis: An Experimental Study, Arch. Surg. **25**:555 (Sept.) 1932.

LOSS OF PROTEIN FROM THE BLOOD STREAM

EFFECTS OF THE INJECTION OF SOLUTION OF PITUITARY AND OF EPINEPHRINE

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In previous studies,[1] the composition of the blood with particular reference to the protein content has been determined in experiments in which a decline in blood pressure produced by a variety of means was accompanied by the introduction of fluids. The fluids were injected intravenously in most of the experiments, and they included those frequently used in treating shock. In one group of studies,[1b] an unexplained decline in blood pressure occurred. This drop appeared either before or shortly following the beginning of the introduction of fluid intravenously into normal anesthetized dogs. Usually the arterial pressure remained depressed for only a short time and then returned to the previous control level. The decline in blood pressure occurred in a few of the experiments in which solutions of salt or of dextrose were used, and in most of those in which an unpurified solution of acacia was injected. In all of the experiments in which the blood pressure declined, the introduction of the fluid was accompanied by a decrease in the

absolute amount of plasma protein. In other experiments,[1c] a decline in blood pressure was produced by the subcutaneous injection of histamine. The introduction of fluids into these animals was accompanied by a decrease in the absolute amount of plasma protein. That a decline in blood pressure per se is not the sole factor responsible for the loss of protein was shown in additional experiments [1c] in which the effects of hemorrhage and the introduction of fluids were studied. The decline in blood pressure in these experiments was not accompanied by loss of protein, except for that removed in the blood. When a drop in blood pressure was produced by the injection of procaine hydrochloride into the spinal canal, the loss of protein was not great.

The present experiments were undertaken in order to determine whether or not the loss of protein that was found in the experiments in which the unexplained declines in pressure appeared and in those in which histamine was injected could be prevented by the injection of solution of pituitary and of epinephrine. Concerning the actions of these drugs Krogh[2] stated:

A minimal dose of adrenalin, injected into the blood or added to a perfusion fluid, normally diminishes the flow of blood to the organs studied, and such an effect is without doubt brought about by constriction of arterioles. Pituitrine, on the other hand, appears to have no effect in minute dose on the rate of inflow of blood, but a distinct effect on the blood color, brought about by constriction of the skin capillaries and venules.

METHODS

Dogs were used in all experiments. Morphine sulphate was employed as the narcotic. The studies included determinations of the blood pressure, hemoglobin and hematocrit readings and of the content of the blood serum in total protein, albumin and globulin. In the control studies, the blood volume was also determined. In subsequent studies, alterations in the blood volume were calculated from changes in the hemoglobin and hematocrit readings. In some of the experiments, the decline in blood pressure was produced by the introduction of from 6 to 10 cc. of 6 per cent unpurified acacia solution into the external jugular vein. In several instances the replacement of the blood that was removed for the control studies was associated with a decline in the blood pressure. In the remaining experiments, the decline in blood pressure was produced and maintained by the repeated subcutaneous injection of histamine. Simultaneously with the beginning of the decline in blood pressure, physiologic solution of sodium chloride was introduced intravenously at the rate of 10 cc. per kilogram of body weight per hour, and this was continued for four hours. The drugs were administered in three different ways. In some experiments, the solution of pituitary or epinephrine was placed in the salt solution that was injected intravenously. In other instances the drug was introduced intravenously in fairly large amounts during the early part of the experiments without diluting it with salt solution. In the remaining experiments, the administration was by the subcutaneous route. The total quantities of solution of pituitary and of epinephrine that were given in the various experiments varied

2. Krogh, A.: The Anatomy and Physiology of the Capillaries, New Haven, Conn., Yale University Press, 1929.

TABLE 1.—*Effects of the Intravenous Injection of Physiologic Solution of Sodium Chloride Containing Solution of Pituitary in the Presence of an Unexplained Decline in Blood Pressure*

Experiment	Time from Beginning	Amount of Fluid Given, Cc.	Pituitary Solution, Cc.	Total Protein		Albumin		Globulin		Blood Volume, Cc.			Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
				Serum, per Cent	Entire, Gm.	Serum, per Cent	Entire, Gm.	Serum, per Cent	Entire, Gm.	Red Blood Cells	Plasma	Whole			
T 135 16.3 Kg.	Control	0	...	6.60	69.0	2.71	28.6	3.89	41.0	(642)	(1,054)	(1,696)	37.9	88.8	120
	1 hr.	163	...	6.40	45.5	2.50	17.8	3.90	27.7	670	712	1,382	48.5	109.0	58
	2 hr. 30 min.	407	...	5.47	49.5	2.28	20.6	3.19	28.9	682	905	1,587	43.0	94.9	94
	4 hr.	652	1.6	5.34	51.7	2.21	21.5	3.13	30.2	695	970	1,665	41.8	90.5	74
	5 hr. 30 min.	...	...	5.78	51.2	2.42	21.4	3.36	29.8	699	886	1,585	44.1	95.0	74
	7 hr.	...	...	5.96	54.2	2.45	22.3	3.51	31.9	728	910	1,638	44.5	92.0	75
	Injected blood	...	...	6.98	...	3.50	...	3.48	...	...	...	.....	33.4	71.0	
T 136 14.4 Kg.	Control	0	...	6.14	59.0	3.63	34.8	2.52	24.2	(440)	(960)	(1,400)	31.5	71.8	96
	1 hr.	144	...	6.37	27.2	3.39	14.5	2.98	12.7	470	428	898	52.3	111.9	50
	2 hr. 30 min.	360	...	5.61	25.7	2.88	12.2	2.63	12.5	480	458	938	51.2	107.1	70
	4 hr.	576	1.4	5.30	27.2	2.81	14.4	2.49	12.8	491	514	1,005	49.0	100.0	70
	4 hr. 50 min.	...	...	5.62	28.1	2.70	14.0	2.83	14.2	502	500	1,002	50.2	101.0	22
	Injected blood	...	...	5.70	...	2.39	...	3.31	...	...	...	.....	42.5	98.2	
T 137 19.0 Kg.	Control	0	...	6.50	76.7	2.70	31.8	3.80	44.9	(775)	(1,180)	(1,955)	39.7	92.0	106
	1 hr.	196	...	6.01	61.0	2.39	24.2	3.62	36.8	795	1,015	1,810	44.0	99.3	108
	2 hr. 30 min.	490	...	5.88	65.2	2.36	26.3	3.52	38.9	750	1,110	1,890	41.3	95.1	122
	4 hr.	784	2.0	5.61	69.0	2.31	28.4	3.30	40.6	780	1,230	2,010	38.9	89.3	126
	5 hr. 30 min.	...	...	6.24	67.0	2.56	27.5	3.68	39.5	840	1,075	1,915	43.9	93.8	119
	7 hr.	...	...	6.19	68.1	2.56	28.2	3.63	39.9	880	1,100	1,980	44.4	90.9	114
	Injected blood	...	...	4.84	...	2.28	...	2.56	...	...	...	.....	19.9	45.4	

Protocols.—T 135: Decline in pressure was produced by giving 10 cc. of acacia.

T 136: Decline in pressure followed replacement of blood that was removed for control determinations.

T 137: Immediately after the blood that had been withdrawn for the control determinations was replaced, the blood pressure declined to a mean of 48 mm. of mercury and remained at that level for a few minutes.

TABLE 2.—*Effects of the Intravenous Injection of Physiologic Solution of Sodium Chloride Containing Epinephrine in the Presence of an Unexplained Decline in Blood Pressure*

Experiment	Time from Beginning	Amount of Fluid Given, Cc.	Epinephrine, Cc.	Total Protein		Albumin		Globulin		Blood Volume, Cc.			Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
				Serum, per Cent	Entire, Gm.	Serum, per Cent	Entire, Gm.	Serum, per Cent	Entire, Gm.	Red Blood Cells	Plasma	Whole			
T 113 16.1 Kg.	Control	0	...	5.56	44.8	3.13	25.3	2.43	19.5	(421)	(806)	(1,220)	31.5	81.6	118
	1 hr.	164	...	5.38	23.8	2.82	12.2	2.56	11.6	457	413	900	50.8	111.5	80
	2 hr. 30 min.	410	...	4.80	29.1	2.41	11.8	2.30	14.3	459	606	1,065	43.1	91.3	118
	4 hr.	656	1.6	4.39	30.2	2.28	14.3	2.11	15.9	452	488	1,110	39.6	88.2	118
	5 hr. 30 min.	...	...	4.93	32.4	2.04	13.4	2.89	19.0	460	657	1,117	41.2	89.8	116
	7 hr.	...	...	5.11	32.1	2.60	16.3	2.51	15.8	460	628	1,097	42.7	91.5	97
	Injected blood	...	...	6.01	....	3.48	....	2.53	....	...	...	.....	31.2	89.2	
T 115 18.9 Kg.	Control	0	...	6.70	63.3	3.84	36.2	2.86	27.1	(881)	(944)	(1,825)	48.3	116.2	130
	1 hr.	188	...	6.32	55.9	3.48	30.8	2.84	25.1	895	885	1,780	50.3	119.0	120
	2 hr. 30 min.	470	...	6.52	55.4	3.51	30.1	2.98	25.3	915	850	1,765	51.9	120.0	126
	4 hr.	752	1.9	5.90	55.0	3.24	29.7	2.75	25.3	927	918	1,845	50.2	115.0	137
	5 hr. 30 min.	...	...	6.50	55.5	3.45	30.1	2.85	25.1	914	881	1,795	51.2	118.1	125
	7 hr.	...	...	6.32	51.3	3.45	28.0	2.87	23.3	923	812	1,740	53.3	122.0	117
	Injected blood	...	...	7.64	....	3.78	....	3.80	....	...	...	.....	37.0	85.3	

Protocols.—T 113: Morphine was used as anesthetic. A small amount of gum acacia solution was introduced intravenously in order to cause the decline in blood pressure. As soon as a decline in blood pressure was initiated, the introduction of salt solution containing epinephrine was commenced. T 115: Morphine was used as anesthetic. Following the control determinations 7 cc. of 6 per cent gum acacia was introduced intravenously. The blood pressure declined to 75 mm. and remained there for a few minutes. As soon as the blood pressure began to decline, the introduction of salt solution containing epinephrine was commenced.

from 0.1 to 0.3 cc. per kilogram of body weight. The various determinations were performed one hour, two and one-half hours and four hours following the beginning of the introduction of fluids, and also one and one-half hours and three hours following the termination of the injections.

RESULTS

Twenty experiments were performed. The mean arterial blood pressure was maintained at a level of less than 100 mm. of mercury in all of the experiments in which histamine was injected. In approximately one half of the experiments in which the decline in pressure followed the introduction of acacia or of blood, there was a return shortly thereafter to the previous control level. In the remaining experiments the pressure remained definitely depressed. In all experiments there were a decrease in the volume of plasma, a diminution in the percentage of protein and a marked decrease in the absolute amount of plasma protein. The results do not differ from those of the experiments reported previously in which solution of pituitary and epinephrine were not injected. However, it was necessary to use larger amounts of histamine in the present experiments in order to keep the blood pressure at a low level. The results of the experiments in which solution of pituitary or epinephrine was introduced with the salt solution into animals in which the unexplained decline in blood pressure occurred are given in tables 1 and 2. The findings in the other experiments did not differ from these.

SUMMARY

Experiments were performed in which a decline in blood pressure was produced by the introduction of histamine, of unpurified acacia and of incompatible blood, and salt solution was injected continuously intravenously. The introduction of solution of pituitary or of epinephrine in the amounts used in these experiments did not prevent the loss of protein from the circulation.

FORTY-NINTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY·

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MISCELLANEOUS CONDITIONS

Osteochondritis Dissecans Capituli Radii.—Nielsen[22] reported 3 cases of osteochondritis dissecans occurring in the radial head. In each case the defect occurred on the inner articular margin of the head of the radius. There was no history of trauma. Clinically, there were weakness, severe pain in the elbow on motion, blocking motion and muscular atrophy. Roentgenologically and at operation, the typical appearance of the loose body with a defect in the articular surface was observed. In the author's clinic, during the past seven years, operations were performed in these 3 cases of osteochondritis dissecans in the radial head and in 35 cases of osteochondritis dissecans in the humeral head.

Avulsion of the Anterior Superior Iliac Spine.—Rothbart[23] reported, with x-ray illustrations, 2 cases in which the anterior superior spine of the ilium was torn off by indirect violence and displaced. Only 1 other case, reported by Köhler, is recorded in the German literature.

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22. Nielsen, A.: Acta chir. Scandinav. **69**:305, 1932.
23. Rothbart, L.: Zentralbl. f. Chir. **59**:781, 1932.

[ED. NOTE.—One of the editors has recently seen an example of this injury in a stout boy. The injury occurred during a foot race.]

Rupture of the Pectoralis Major.—Borchers and Tontscheff[24] reviewed the clinical findings in rupture of the pectoralis major muscle. This injury is most apt to occur when an external force strikes the muscle at a time when it is in a state of contraction. A visible flattening and loss of function are the outstanding signs of rupture in the muscles.

Mechanics of Muscular Contractures in the Wrist and Fingers.—In discussing muscular contractures of the wrists and fingers, Steindler[25] emphasized the biophysics of the condition and attacked the problem under four headings, as follows: (1) the paralytic contractures, including those due to infantile, obstetric and peripheral paralyses; (2) the innervational contractures represented by the spastic paralyses; (3) the histochemical or ischemic contractures, and (4) the arthrogenic contractures, or those subsequent to an arthritic process and resulting not from the inherent muscle contracture alone, but from gravity and external resistances. The mechanism of development of each type of contracture was carefully discussed. In the treatment of any such contracture, Steindler would exhaust every effort of conservative treatment, consisting of stretching and muscle training, before resorting to operative measures. The procedures for the operative release of contractures mentioned by the author were: (1) lengthening of the tendon, (2) stripping of the tendon, (3) the injection of alcohol and resection of the motor nerve, (4) juxta-articular osteotomies and (5) simple myotomies.

Rupture of the Long Extensor Tendon of the Thumb.—A case of rupture of the tendon of the long extensor of the thumb was reviewed by Lapeyre.[26] The patient, aged 55, suffered from pain and swelling following a fall on the extended wrist. Twelve days later there was a sudden sharp pain in the thumb, and from that time on the second phalanx of the thumb could not be extended. The normal contour of the extensor tendon was absent. The ruptured end of the tendon was not felt. X-ray pictures showed a fracture of the lower end of the radius without displacement. Operation was refused. The author stated that rupture of this tendon falls into two categories: (1) spontanous ruptures without a history of injury; all the cases reported in this group occurred among military drummers; (2) ruptures following trauma, usually a fracture of the lower end of the radius. Twenty-eight cases of spontaneous rupture were reported. The lesions always occurred on the left side

24. Borchers, E., and Tontscheff, P.: Zentralbl. f. Chir. **59**:770, 1932

25. Steindler, A.: J. Bone & Joint Surg. **14**:1, 1932.

26. Lapeyre, J. L.: Presse méd. **40**:456, 1932.

among drummers who had been in service a long time. There was usually a history of swelling on the dorsal surface of the thumb of some duration. Then suddenly there was a slight sharp pain, occasionally a palpable snap, and the drumstick fell out of the hand. Some ruptures were incomplete; others were complete. In all cases it appeared that the tendon had undergone some weakening change, such as a tenosynovitis. Fifty-one cases of traumatic rupture were reported. The majority of patients were elderly. Thirty-nine cases were accompanied by fracture of the lower end of the radius. This fracture was often insignificant. There was an interval of days and sometimes weeks between the injury and the rupture. The movement producing rupture was often slight. The essential symptoms were a slight snap accompanied by very little or no pain, followed by an inability to extend the distal phalanx of the thumb. The site of rupture was always close to the belly of the muscle. The mechanism of these ruptures was not definitely understood. The author believed that following trauma the tendon becomes strangulated in its sheath by rupture of the tenaculum tendinum containing the nutrient blood vessels. Without nourishment the tendon degenerated, became atrophic and ruptured during some slight movement of the thumb. Treatment was surgical, with repair of the ruptured tendon. Conservative methods were successful only in the few cases in which rupture was partial.

Rupture of the Extensor and Flexor Pollicis Longus Tendons Following Colles' Fracture.—Two cases, 1 of rupture of the extensor pollicis longus tendon and the other of rupture of the flexor pollicis longus tendon, were reported, and the literature concerning 27 cases of the former was reviewed by McMaster.[27] The author was unable to find any reported cases of rupture of the flexor pollicis longus tendon. Both of the author's cases followed Colles' fractures. One occurred approximately one month after the fracture, and the second four months after injury. Both came on spontaneously without pain and without direct injury. Disability in using the thumb was the outstanding symptom in both cases. There was no pain. In regard to the cause of this condition, the author suggested two possibilities: (1) partial severance of the tendon by a sharp edge of bone at the time of the fracture, or (2) local tendon necrosis due to a disturbed blood supply. Both patients recovered completely after an open operation.

OPERATIONS ON THE BONES, JOINTS AND TENDONS

Translocation of Tendons.—Von Baeyer[28] described what he called translocation in preference to transplantation of tendons because of the

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27. McMaster, P. E.: J. Bone & Joint Surg. **14**:93, 1932.

28. von Baeyer, H.: Zentralbl. f. Chir. **58**:3140, 1932.

relatively simple technic of the former. The use of this procedure in four situations was discussed: (1) In paralysis of the calf muscles with good peronei, a groove was made in the long axis of the tendo achillis, in the tuberosity of the os calcis on the lateral aspect. The tendon of the peroneus longus was translocated or dislocated into this groove. The tension of the muscle produced an equinus deformity, which disappeared in a few weeks. It soon functioned normally in the new location. (2) In paralysis of the tibialis anterior with a good extensor longus hallucis, a groove was made on the scaphoid in its medial plane. The extensor longus hallucis tendon was translocated into this groove, and the foot was immobilized in supination with the great toe in a neutral position. (3) In palsy of the quadriceps muscle, the sartorius was attached to the atrophic patellar ligament, and one or the other of the internal hamstrings was also transplanted. (4) In habitual dislocation of the shoulder, the long tendon of the biceps was freed and the intertubercular sulcus of the humerus was deepened and lengthened to the center of the humeral head. The tendon of the long head of the biceps muscle was translocated into this groove.

[Ed. Note.—Procedures 1 and 2 are new to the editors. Procedure 3 is a tendon transplantation which is carried out in many clinics in this country and abroad. Procedure 4, while similar to the Nicola operation, has the disadvantage of injuring the articular cartilage.]

Plastic Repair of the Anterior Crucial Ligament.—Porzelt [29] devised a procedure for the repair of the anterior crucial ligament. A pedicled ligament was obtained from the inner aspect of the joint capsule, leaving it attached at its base. This ligament was brought through the tibia and sewed to the portion of the anterior crucial ligament still attached to the femur. The articular capsule was repaired. Good functional results were reported.

[Ed. Note.—It is questionable whether operations that attempt repair of the crucial ligament to correct instability of the knee joint should be advocated. In the cadaver, at least, the lateral ligaments seem to be of much more importance, since division of the anterior crucial ligament through a punctate incision in the capsule by one of the editors produced little instability. The recovery of stability in the joint after rupture of a crucial ligament seems to depend chiefly on the lateral ligaments of the knee joint and on muscle tone.]

Operation for Obstetric Paralysis.—Kleinberg [30] reported 8 cases of obstetric paralysis, of the upper arm type, in which he performed an operation consisting of subperiosteal reflection of the external rotators

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29. Porzelt, W.: Zentralbl. f. Chir. **59**:658, 1932.

30. Kleinberg, S.: Reattachment of the Capsule and External Rotators of Shoulder for Obstetric Paralysis, J. A. M. A. **98**:294 (Jan. 23) 1932.

and a portion of the capsule of the shoulder joint for a distance of two-thirds the circumference of the humerus. The subscapularis was also resected subperiosteally. The arm was put in a position of abduction and external rotation. The structures then reattached themselves in their new positions. In the discussion which followed, Sever pointed out the importance of also dividing the pectoralis major tendon, and he said that frequently the coracobrachialis was a deforming factor.

Surgical Approach in Old Posterior Dislocation of the Elbow.— Van Gorder [31] described his technic for operative reduction of an old posterior dislocation of the elbow. It consisted essentially in dividing the triceps tendon transversely one-half inch (1.27 cm.) above the olecranon. The ulnar nerve was exposed and carefully protected. Adhesions were then freed and the dislocation gently reduced. The divided triceps tendon was then sutured either with fascia lata or with a portion of the Achilles tendon. Active exercises were started two weeks after operation. Five cases were presented, with illustrations.

Operative Procedures for Paralytic Talipes Calcaneus.—Whitman [32] was opposed to transplantation of the tibialis posticus and peronei muscles for the correction of paralytic talipes calcaneus as advocated by Lange.[33] He advised astragalectomy for this condition. He considered the astragalus the key of the deformity, and he thought that backward displacement of the foot and the contact between the tibia and fibula and the tarsal bones secured lateral stability and checked dorsal extension of the foot, thus supplying the resistance essential for normal gait. He referred to Miltner,[34] who, in 112 cases in which astragalectomy was performed, reported good results in 101 cases, fair results in 6 and poor results in 5.

<center>FRACTURES</center>

Marching Fractures of the Metatarsal Bones.—Straus [35] reported a case of unrecognized marching fracture, or spontaneous fracture of the second metatarsal bone, in an obese woman. X-ray pictures taken before operation showed no fracture, but new bone formation. An exploratory operation showed an old transverse fracture of the metatarsal bone surrounded by callus. The author reviewed various hypotheses concerning the etiology. He suggested that if the fatigued muscles failed to support the osseous structures of the foot, fracture might occur.

31. Van Gorder, G. W.: J. Bone & Joint Surg. **14**:127, 1932.

32. Whitman, R.: J. Bone & Joint Surg. **14**:242, 1932.

33. Lange, F.: J. Bone & Joint Surg. **13**:479, 1931

34. Miltner, L. J.: J. Bone & Joint Surg. **13**:502, 1931.

35. Straus, F. H.: Surg., Gynec. & Obst. **54**:581, 1932.

[Ed. Note.—This case is of interest, since amputation of the foot was suggested on the assumption that a malignant condition existed. These cases may simulate malignant periosteal lesions and may be so diagnosed because a history of trauma is absent.]

Treatment of Central Luxation of the Femur.—Babini [36] discussed the treatment in central dislocation of the femoral head. Two cases were reported in which the lesion followed a severe fall on the greater trochanter of the affected side. Reduction, with a satisfactory end-result, was obtained in both cases by skeletal traction on the greater trochanter with counter-traction on a plaster spica.

Fractures of the Knee, "Bumper Type."—Carey [37] described a method of closed reduction in fractures about the knee commonly called the "bumper type." The method consisted of manual reduction of the fibular head and replacement and reshaping of the tibial condyle with a mallet. Plaster immobilization was continued for three weeks, when physical therapy was begun. Weight bearing was permitted in from nine to eleven weeks. Forty-five cases were reviewed. The mechanics of the production and associated injuries were discussed. The author thought that a rupture of the external lateral ligament should be assumed to be present in many cases.

[Ed. Note.—In the editors' experience, the internal lateral ligament is the one usually injured.]

Treatment of Compression Fractures of the Articular Surface of the Tibia.—Hultén [38] stated that pain occurred about the knee if a condyle of the tibia was permanently displaced downward from 0.5 to 1 cm. after fractures. When attempts at closed reduction did not secure the normal anatomic relationship, open reduction was advocated. For old cases he described a method of driving in a bone wedge from the tibia into the lowered condyle to level the condyles.

Longitudinal Fractures of the Patella.—Lapidus [39] called attention to the not infrequent occurrence of longitudinal fracture of the patella, and pointed out that such an injury frequently went unrecognized because of failure to take proper x-ray pictures. The writer reviewed the literature and collected the cases of 13 patients treated by himself or his colleagues in two years. In 9 of these cases the fracture was in the usual place, i. e., in the junction of the outer and middle quarters of the patella. He thought that most such fractures were produced indirectly by muscular pull with the knee flexed, thus producing pressure between the femoral condyle and the outer pole of the patella. It was

36. Babini, R.:   Chir. d. org. di movimento **16**:546, 1931.

37. Carey, N. A.:   California & West. Med. **36**:226, 1932.

38. Hultén, O.:   Zentralbl. f. Chir. **59**:344, 1932.

39. Lapidus, P. W.:   J. Bone & Joint Surg. **14**:351, 1932.

important to differentiate such a fracture from a congenital anomaly. In order to demonstrate a longitudinal fracture of the patella, he suggested taking a roentgenogram by placing the anterior aspect of the thigh on the x-ray film and flexing the leg on the thigh.

Os Trigonum and Fractures of the Posterior Aspect of the Astragalus.—Ghigi and Morelli [40] dissected 80 cadavers, and in 35 feet a posterior astragalar process longer than 5 mm. was found. In 16 feet a smaller process was noted. In 2 cases a posterior process was covered with articular cartilage. In only one instance was an os trigonum found. The authors, therefore, found a well developed posterior astragalar process in 21.8 per cent of the ankles. Sixteen cases, 1 bilateral, of fractures of the posterior astragalar process were reported, 9 in detail. Several cases occurred in conjunction with adjacent fractures. The fractures caused acute pain in the ankle, swelling and tenderness. Complete recoveries followed immobilization. Shepher, in 1882, first described this fracture. A review of the literature was given.

Late Results in Fractures of the Olecranon.—Madlener and Wienert [41] reviewed 36 cases of fracture of the olecranon. In 24 of these cases an operative reduction was performed, and 12 patients were treated conservatively. Wire was used for suture in the operative reductions. Better functional results were observed in the patients treated conservatively. In the group requiring operation, the results were good in only slightly more than half of the cases. In 14 of 22 patients examined from two to nine years after treatment, an arthritis deformans had developed.

Colles' Fracture.—Carp [42] analyzed the roentgen findings in 100 cases of Colles' fracture accompanied by fracture of the ulnar styloid and correlated them with anatomic dissections in an effort to ascertain the cause of the fracture of the ulna. He concluded that fractures at the base of the ulnar styloid were due to the pull of the displaced intra-articular fibrocartilage of the wrist joint, and at the middle and tip of the styloid by the pull of the ulnar collateral ligament.

Slipping of the Upper Femoral Epiphyses.—Ferguson and Howorth [43] reported their observations in 70 cases of slipping of the upper femoral epiphysis observed at the New York Orthopedic Hospital. Sixty-three cases were seen in adolescent patients, while 7 were observed

40. Ghigi, G., and Morelli, A.: Chir. d. org. di movimento **16**:499, 1931.

41. Madlener, M. J., and Wienert, B.: Arch. f. klin. Chir. **168**:577, 1932.

42. Carp, L.: The Roentgenologic Displacements in Colles' Fracture: With Special Reference to the Mechanism of the Accompanying Fracture of the Ulnar Styloid; A Report of One Hundred Consecutive Cases, Arch. Surg. **24**:1 (Jan.) 1932.

43. Ferguson, A. B., and Howorth, M. B.: Slipping of the Upper Femoral Epiphysis: A Study of Seventy Cases, J. A. M. A. **97**:1867 (Dec. 19) 1931.

in "adult residuals." Fifteen cases were bilateral. The age of onset ranged from 8 to 15 years. Only 65 per cent of the patients were overweight. Trauma, as a rule, was trivial as an etiologic factor. The theory of infection was suggested as a possible cause. The early signs and symptoms in the "preslip stage" were enumerated, and the means of diagnosis both from the physical examination and from the x-ray plate were described. In regard to treatment, of 21 attempted closed reductions, 18 failed, 6 cases later coming to open operation. In 11 cases open reduction was attempted, with fair anatomic success in only 3. In five of the 11 cases the head was freed at the epiphyseal line, while in 6 cuneiform osteotomy was performed near the epiphyseal line. In 4 cases subtrochanterian osteotomy was done when there was a displacement of from five-eights to seven-eighths inch (0.9 to 1.5 cm.). The authors favored the open operation, with drilling of the femoral neck across the epiphyseal line in young patients in the preslip stage. They felt that no serious interference with growth would occur. They regarded the preslip stage as a real emergency, and favored absolute rest in bed or open operation with drilling.

Repair of Ununited Fractures of the Neck of the Femur.—Magnuson [44] advocated an operation which he believed restored the normal weight-bearing lines and anatomy more nearly than the various other operations designed to improve this common disabling condition. The ununited head of the femur was hollowed out with a burr so as to form a cup the deepest part of which was pointing upward rather than at the center of the hip joint. The trochanter was then removed, and the stump of the neck was remodeled so as to fit into the cup-shaped head. The trochanter was then reattached to the femoral shaft. Weight bearing was started in eight weeks.

Lateral Dislocation of the Vertebrae.—Lawson [45] reported 3 cases of lateral dislocation of a vertebra. The first and third patients were seen shortly after injury, while the second patient was observed four months after the original trauma. An attempt was made to reduce the dislocation by open operation in the first instance, but this was unsuccessful. The second patient was untreated, and no mention was made of the treatment in the third case. In all cases, accompanying the dislocation there was extensive damage to the laminae and the transverse processes. In the first case, the dislocation was of the fourth lumbar segment on the fifth sacral vertebra; the second case presented dislocation of the fifth lumbar segment on the first sacral vertebra.

Vertebral Fractures Without Injury to the Cord.—In a series of 215 patients with fractures involving the spinal column collected by

44. Magnuson, P. B.: The Repair of Ununited Fracture of the Neck of the Femur, J. A. M. A. **98**:1791 (May 21) 1932.

45. Lawson, J. D.: J. Bone & Joint Surg. **14**:387, 1932.

Conwell.[46] there were 100 patients with vertebral fractures without injury to the cord. From these 100 cases he drew the following conclusions: Immediate splinting of the injury is important; when a spinal fracture is suspected, the patient should be transported prone. Negative x-ray pictures immediately after injury do not always rule out fracture; in a number of cases, later vertebral collapse may be observed. Complete reduction of the fracture is desirable, but is not always necessary for a good functional result. Later collapse may occur after reduction.

Operative fusion is indicated, particularly if there is delayed healing of the fracture and severe persistent pain. Fusion, however, does not always relieve the pain. Osteo-arthritis is commonly observed as a complication in patients over 40. Manipulative reduction under general anesthesia is necessary in only a few cases. In most instances reported, gradual hyperextension of the spine was used, with an adjustable convex Bradford frame, for fractures with compression of the anterior portion of the vertebral bodies. When reduction was accomplished, a plaster case was molded to the body. · Conwell advised immediate reduction of the fracture dislocation of the cervical vertebrae, followed by fixation in a plaster cast. When there is great danger of injury to the cord, he advised constant traction. Dislocation of the dorsal and lumbar vertebrae is best treated by constant traction.

Manipulative Reduction in Fractures of the Spine.—Davis[47] gave the subsequent course in several cases of spinal fracture followed up for five years in which his method of combined passive and active hyperextension of the spine was used. No late changes occurred in the reduced spinal fractures. Emphasis was placed on an immediate decision in fracture of spines with paralysis as to whether laminectomy or reduction should be done. The author thought that in the great majority of cases reduction of the impacted fracture of the centrum of the vertebra, thereby enlarging the neural canal, is of more importance than laminectomy, as it accomplishes a similar purpose without altering the deformity.   .

[ED. NOTE.—The value of Davis' manipulative reduction of spinal fractures is unquestioned. Since his original article many cases have been handled successfully by others. This method, without doubt, shortens convalescence and is accompanied by a higher percentage of complete recoveries.]

New Method of Treating Fractures Using the Well Leg for Counter-Traction.—Anderson[48] described a method of treating fractures of the pelvis, femur and tibia in which skeletal traction is made

46. Conwell, H. E.:   South. M. J. **25**:141, 1932.

47. Davis, A. G.:   Am. J. Surg. **15**:325, 1932.

48. Anderson, R.:   Surg., Gynec. & Obst. **54**:207, 1932.

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EXPERIMENTAL OBSTRUCTIVE JAUNDICE

ITS EFFECT ON FIBRINOGEN AND COAGULATION OF THE BLOOD

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NEW ORLEANS

The scientific explanation of the hemorrhagic tendency in patients suffering with jaundice has been energetically sought for by a great number of investigators, some of whom are apparently definitely convinced by the results of their experimental work that the problem is settled. It is difficult for one reviewing the literature to come to any definite conclusion in his own mind relative to this phenomenon, because of the wide diversity of opinions and because of the conflicting data in the literature.

The fibrinogen content of the blood plasma has not been investigated carefully from an experimental standpoint as a possible cause for this hemorrhage, and it was with that in mind that the work herein submitted was done in an attempt to arrive at some solution of this perplexing and vexing problem.

After considering this subject theoretically, it seems that the hemorrhagic tendency in these patients might be attributed to the presence of abnormal amounts of fibrinogen, which plays such a prominent rôle in the coagulation of the blood. It is conceded that the greater part of the blood fibrinogen has its origin in the liver, and the fibrinogen content of the plasma has been shown to vary with conditions of the liver. It is assumed, of course, that obstruction to the outflow of bile by the normal route causes more or less hepatic damage.

The restoration of fibrinogen to its normal level in the blood after depletion from any cause, e. g., bleeding, is almost exclusively accomplished by the liver, as was indicated by Howe.[1] Mann and Bollman[2] demonstrated that following complete extirpation of the liver the fibrinogen of the blood did not return to its normal level after bleeding. Recent investigations, particularly those of Howe,[3] point to the liver as the main source of supply of fibrinogen.

1. Howe: J. Biol. Chem. **57**:235 (Aug.) 1923.
2. Mann and Bollman: Proc. Staff Meet., Mayo Clin. **4**:329 (Nov.) 1929.
3. Howe: Physiol. Rev. **5**:439, 1925.

capillary pressure or injury' (Landis[11]). The viscosity of fibrinogen is known to be greater than that of the serum proteins, and the permeability of hepatic endothelium is said to be greater than that of any other endothelium. Wiener and Wiener,' after an exhaustive study of fibrinogen and serum proteins in man, concluded that the physiologic limits of the concentration of fibrinogen in the plasma are at wide variance. Their reports, from investigation of the amounts of these substances in various physiologic and pathologic conditions, show that the fibrinogen is slightly increased during menstruation and definitely increased during the later months of pregnancy and during the puerperium. They concluded further that any irritation of the liver, i. e., slight infections, exposure to the x-rays, ingestion of chloroform and phosphorus in small doses and all inflammatory processes, produces an increase in the fibrinogen content of the plasma. In cirrhosis of the liver, they found a slight increase early in the process, but a decrease or low normal fibrinogen content later, whereas concurrent infections elsewhere in the body caused only slight increases. In the presence of jaundice without pyrexia, the concentration of fibrinogen was found to be within normal limits. In cholecystitis, the findings are similar to those in infections. Pickering[12] also noted a definite decrease in fibrinogen content of the plasma in cases of cirrhosis of the liver. Whipple and Hurwitz[13] showed that small doses of chloroform and phosphorus increase the coagulability of the blood and increase the fibrinogen content of the plasma, but that large doses of these "liver poisons" produce the opposite effect.

There has been a great deal of controversy among investigators in the clinical field, as well as among those in the experimental laboratory, concerning the cause of hemorrhage in jaundiced patients. Most of the work that has been done has been to determine whether or not fluctuation in the calcium content of the serum occurs, and whether or not these changes affect coagulability of the blood in jaundiced patients.

In reviewing the literature it is difficult, because of the vast difference in opinions, for one to obtain any established facts concerning the effect that calcium content of the blood has on coagulability. These opinions are based on results obtained in the clinic and the laboratory; thus it is impossible to conclude that any constant relationship exists. Halverson, Mohler and Bergeim[14] reported a slight reduction in calcium

11. Landis: Am. J. Physiol. 81:124, 1927.
12. Pickering: The Blood Plasma in Health and Disease, New York, The Macmillan Company, 1928, p. 24.
13. Whipple and Hurwitz: J. Exper. Med. 13:136, 1911.
14. Halverson; Mohler, and Bergeim: Calcium in the Blood in Tuberculosis, J. A. M. A. 68:1309 (May 5) 1917.

Whipple attributed the origin of fibrinogen to the liver. Foster and Whipple[4] found that the fibrinogen content of the plasma is reduced by measures that cause destruction of hepatic tissue. McMaster and Drury[5] further confirmed the fact that fibrinogen is of hepatic origin. The blood of normal animals was defibrinated and reinjected, and it was found that 90 per cent of the normal fibrinogen content was present in six hours. When hepatectomized animals were treated in the same way, there was noted a slight rise of fibrinogen in from four to five hours, presumably from a reserve in the tissues, but after from four to five hours the fibrinogen content decreased until death. It was concluded that without the liver the organism apparently has no power to regenerate fibrinogen.

On the basis of the aforementioned results and similar personal observations, Hull,[6] McLester[7] and many others concluded that the fibrinogen content of the plasma may be used as an index to hepatic function. Peters and Van Slyke[8] contended that decrease in fibrinogen content does not parallel the degree of destruction of the liver. They admitted, however, that severe injury to the liver is, in a number of cases, attended with decrease in plasma fibrinogen. Foster and Whipple[4] showed that inflammatory and destructive lesions of the liver cause an increase in fibrinogen as would a normal stimulus. When the loss of liver substance is so great that the organ can no longer meet the demands of the body, fibrinogen decreases.

Wiener and Wiener[9] conceded that changes in the permeability of the endothelium may be responsible for, or may influence, the change in concentration of fibrinogen in the plasma. Peterson assumed that the capillaries govern permeability by highly specialized function. Their endothelial walls act as an "ultrafilter," and any changes in their structure should result in altered concentrations of the various materials that are allowed to pass. Permeability of the capillaries depends on permeability of the endothelial cells in the walls of the vessels. An increase in this permeability may be caused by dilatation from physical, nervous or chemical stimuli (Krogh[10]) and by increased

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4. Foster and Whipple: Am. J. Physiol. **58**:407, 1922.

5. McMaster and Drury: Proc. Soc. Exper. Biol. & Med. **26**:490, 1929.

6. Hull: Verhandl. d. Kong. f. inn. Med. **33**:201, 1921.

7. McLester: Diagnostic Value of Blood Fibrin Determinations with Special Reference to Disease of the Liver, J. A. M. A. **79**:17 (July 1) 1922.

8. Peters and Van Slyke: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931.

9. Wiener and Wiener: Plasma Proteins, Arch. Int. Med. **46**:236 (Aug.) 1930.

10. Krogh: Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1923, p. 230.

content of blood serum in jaundice. The reduction noted was considered more apparent than real. Koechig[15] arrived at the same conclusion. Walters and Bowler,[16] Snell, Greene and Rowntree[17] and Zimmerman[18] found no change in serum calcium in obstructive or other types of jaundice. Kirk and King[19] reported moderate reductions in total calcium, but greater reductions in diffusible calcium, emphasizing the importance of the rôle that the diffusible, or ionizable, calcium plays in coagulation. Emerson[20] corroborated the findings of Kirk and King by a series of experiments, and called attention to the fact that the probable source of error obtained by other investigators was the disregard of the effect of ether anesthesia. He demonstrated that specimens of blood taken during or shortly after ether anesthesia show an increase in calcium content of the serum. The experimental results obtained by Emerson are not fraught with this error. He showed that in jaundice the serum calcium is diminished concomitantly with diminished coagulability of the blood, and he was able to restore calcium to the normal level by administration of calcium salts in therapeutic doses. Emerson also found an increase in serum calcium in animals with biliary fistulas. Buchbinder and Kern[21] found no alteration in serum calcium after ligation of the common bile duct of the adult dog, but a progressive decrease after the same procedure in the puppy. Subsequently, these same authors found that, after producing obstructive jaundice in thyroparathyroidectomized animals, there resulted a diminution or an absence of tetany. The period of survival of the animals suffering with tetany was prolonged if the jaundice was maintained over a considerable length of time. If, after removal of the parathyroid glands, the animals were subjected to "acute" jaundice, they suffered with severe and terminal tetany. The conclusion was drawn that tetany was altered by obstructive jaundice, on the basis of (1) the response of the thyroparathyroidectomized animal, (2) the relief from tetany following intravenous injection of bile and (3) the absence of tetany in late obstructive jaundice in the puppy with calcium at the tetanic level. One is here reminded of the action of bile as a depressant of the central

15. Koechig: J. Lab. & Clin. Med. **9**:679 (July) 1924.

16. Walters and Bowler: Surg., Gynec. & Obst. **39**:200 (Aug.) 1924.

17. Snell; Greene, and Rowntree: Diseases of the Liver: Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, Arch. Int. Med. **36**:273 (Aug.) 1925.

18. Zimmerman: Am. J. M. Sc. **174**:379 (Sept.) 1927.

19. Kirk and King: J. Lab. & Clin. Med. **11**:928 (July) 1926.

20. Emerson: J. Lab. & Clin. Med. **14**:122 (Nov.) 1928.

21. Buchbinder and Kern: Experimental Obstructive Jaundice: II. Modification of the Parathyroid Tetany Mechanism in Jaundice, Arch. Int. Med. **41**:754 (May) 1928.

nervous system; i. e., it raises the threshold of nervous excitability. Snell and Greene [22] emphasized the fact that there is no agreement concerning the variation in the calcium content of the serum in jaundice. They found that in jaundice all the fractions of the serum calcium— the total, the nondiffusible and the diffusible—are equally affected. They concluded that the amount of alteration in the diffusible calcium of jaundiced patients is not significant. The coagulation time was not considered by Snell, Greene and Rowntree, but they expressed the belief that it is affected by calcium in some more complicated mechanism rather than directly. The variation in dogs and patients was reported insignificant. Gunther and Greenberg [23] stated that a review of the literature produced no proof of a deficiency of available calcium in the blood of jaundiced patients, nor any direct proof of a deficiency of diffusible calcium in the serum. They observed in jaundiced patients a diminution in the nondiffusible calcium, but parallel with this was a loss of serum albumin accounted for by a decrease in total serum proteins. They contended that this cannot be interpreted as an indication of a deficiency of available calcium. They found that the concentration of nondiffusible calcium was low in a few patients with jaundice, but that there was an accompanying lowered concentration of serum albumin, and that the concentration of neither serum albumin nor nondiffusible calcium fluctuated with the degree of jaundice. The nondiffusible fraction of serum calcium was considered to be low as a result of the low serum albumin. It was shown that the value of diffusible calcium is a more accurate measure of the physiologically available calcium than the value of either the nondiffusible or the total calcium fraction in the serum. Gunther and Greenberg contended that factors other than alteration in the amount of available calcium must be sought for to explain satisfactorily abnormal bleeding in jaundiced patients. Waltman Walters,[24] recently, in an excellent treatise on obstructive jaundice, presented evidence to the effect that calcium, given in therapeutic dosage, is rapidly excreted by the kidneys. It does not accumulate in the blood, and the normal level of the serum calcium is restored in two hours.

Ravdin, Riegel and Morrison [25] compared the relative merits of calcium and dextrose as hemostatic agents in the presence of jaundice, and agreed with Bancroft, Kugelmass and Stanley-Brown [26] that coagu-

22. Snell and Greene: Am. J. Physiol. **92**:630 (April) 1930.

23. Gunther and Greenberg: I. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, Arch. Int. Med. **45**:983 (June) 1930.

24. Walters, Waltman: Obstructive Jaundice: Physiological and Surgical Aspects, Rochester, Minn., Mayo Foundation, University of Minnesota, 1931.

25. Ravdin; Riegel, and Morrison: Ann. Surg. **91**:801 (June) 1930.

26. Bancroft; Kugelmass, and Stanley-Brown: Ann. Surg. **90**:161, 1929.

lation and bleeding times are of little value in determining a hemorrhagic tendency. They claimed that, in spite of the agitation favoring the use of calcium in cases of obstructive jaundice, no one has clinically demonstrated a deficiency of serum calcium in these cases. Dextrose is used, and it was suggested that it may help in restoration and repair of the damaged liver. They cited Minot and Cutler's [27] demonstration of the beneficial effect of the use of calcium in dogs with hepatic degeneration, in the blood of which there occurred, as a result of this disease, an increase in guanidine and like substances. They took issue with Partos and Svec [28] in their contention that hyperglycemia results from the use of calcium, on the ground that it does not occur consistently. Nevertheless, they found that calcium therapy was efficacious in diminishing the damage to the liver produced by biliary obstruction. Schreiber [29] and Kehr [30] suggested the use of dextrose preoperatively in cases of jaundice. Since 1920, the use of this substance has become widespread. Walters [31] and Whipple [32] advocated the use of dextrose and calcium and considered dextrose of primary importance as regards the reduction of mortality from surgical operations. Davis, Hall and Whipple [33] asserted that a diet high in carbohydrate would affect regeneration of hepatic tissue at the rate of 100 Gm. daily. Ravdin et al.[25] stated that a diet high in carbohydrate causes more rapid restoration of hepatic structure after release of biliary obstruction and exerts a definitely favorable effect while obstruction exists. They stated that clinical patients whose blood has a prolonged clotting time have severe hepatic damage. Mann, Bollman and Markowitz [34] showed in hepatectomized animals that there occurs: (1) a variable change in coagulation of the blood; (2) a diminution of fibrinogen content, after depletion of the latter from hemorrhage, with partial or no restoration of the same, and (3) no parallelism between fibrinogen content and coagulability of the blood. The latter point was confirmed by work on normal and jaundiced dogs by Ravdin, Riegel and Morrison.[25] Minot and Cutler [27] demonstrated in dogs an increase in guanidine content of the blood associated with hypoglycemia in the presence of jaundice. Ellis [35] showed that

27. Minot and Cutler: Proc. Soc. Exper. Biol. & Med. **26**:607, 1929.

28. Partos and Svec: Arch. f. d. ges. Physiol. **218**:209, 1930.

29. Schreiber: Zentralbl. f. Chir. **2**:1200, 1913.

30. Kehr: Ergebn. d. Chir. u. Orthop. **8**:471, 1914.

31. Walters: Surg., Gynec. & Obst. **33**:651, 1921.

32. Whipple: S. Clin. North America **1**:373, 1921.

33. Davis; Hall, and Whipple: The Rapid Construction of Liver Cell Protein on a Strict Carbohydrate Diet Contrasted with Fasting: Mechanism of Protein-Sparing Action of Carbohydrate, Arch. Int. Med. **23**:689 (June) 1919.

34. Mann; Bollman, and Markowitz: Am. J. Physiol. **90**:445, 1929.

35. Ellis: Biochem. J. **22**:353 and 930, 1928.

dextrose protects the experimental animal from toxemia due to guanidine, definitely proving that it is of value in a restorative rôle. Partos and Svec [28] proved that substances which increase the coagulability of the blood mobilize glycogen and produce hyperglycemia, and that substances prolonging the coagulation time cause hypoglycemia. Cannon and Gray [36] showed that epinephrine causes increase in blood sugar and increase in coagulability of the blood. Rabinovich [37] demonstrated that the coagulation time was diminished following anesthesia, and emphasized the fact that during the first fifteen minutes of anesthesia the blood sugar increases. Boldyreff,[38] followed by Turcatti,[39] expressed opinions opposite to these. Boldyreff stated that with complete loss of pancreatic secretion there is a rise in blood sugar with diminution in coagulability of the blood. Ravdin, Riegel and Morrison [25] stated that hyperglycemia does not increase the coagulability of the blood in all cases, but that hyperglycemia and increase in the coagulability of the blood are present in a great many cases. They suggested that dextrose has the effect of stimulating the formation of fibrinogen, but their experimental data do not bear out this assumption. Svec [40] injected insulin into experimental animals, producing hypoglycemia, which was followed by diminution in coagulability of the blood. Partos [41] confirmed these results, and showed that diabetic animals had increased coagulability of the blood. He was able to produce similar effects by administration of epinephrine hydrochloride to one series of depancreatized dogs and morphine to another series. Walters [24] stated that he considers the preoperative administration of dextrose to be of extreme importance in these cases. He also favors small doses of calcium chloride (5 grains [0.32 Gm.]), intravenously, for three days prior to operation.

Heparin has been investigated in Howell's laboratory. Howell [42] said that diminution of the heparin in the blood is probably the cause of bleeding in hemophilia, jaundice and other such pathologic conditions. This cannot be proved, however, until a method has been devised for quantitative estimation of heparin. Heparin is present in the blood in such small quantities that it is difficult to obtain it even qualitatively. Up to the present time there has been no method submitted for its quantitative determination.

36. Cannon and Gray: Am. J. Physiol. **34:**232, 1914.

37. Rabinovich: Brit. J. Exper. Path. **8:**343, 1927.

38. Boldyreff: Am. J. M. Sc. **177:**778, 1929.

39. Turcatti: Compt. rend Soc. de biol. **100:**116, 1929.

40. Svec: Arch. f. d. ges. Physiol. **224:**62, 1930.

41. Partos: Arch. f. d. ges. Physiol. **224:**448, 1930.

42. Howell: Am. J. Physiol. **77:**689 (Aug.) 1926.

Howell and Holt [43] showed that heparin does not react with calcium salt, but that there is a thermolabile substance in the blood that reacts with the heparin to form antithrombin. This thermolabile substance can be destroyed by raising the temperature of the blood to 70 C., whereas heparin is not destroyed at 100 C. These authors expressed the belief that heparin is present in the blood under normal conditions. They contended that it is an activator for pro-antithrombin, preventing the formation of thrombin in the normal circulation. By this mechanism, the fluidity of the blood is maintained in the undisturbed vascular system. Heparin also prevents the activation of prothrombin to thrombin, according to Howell and Holt.[43] Thus, by means of a double mechanism, this substance is responsible for the prevention of intravascular clotting. Howell [42] expressed the belief that the presence of an abnormal amount of heparin may be responsible for the hemorrhagic tendency of patients with hemophilia and jaundice.

Howell,[44] in a still later publication, again claimed for heparin all the possibilities for which he contended in the previous article. He showed that it was increased in the blood by intravenous injection of peptone. He also found that in shed blood its action was neutralized by the phosphatid material furnished by the corpuscles or tissue cells. Howell found that the antithrombin is increased by intravenous administration of heparin.

Stuber and Lang [45] stated that heparin inhibits coagulation of the blood by inhibition of glycolysis. They observed that, following its injection, there was a decrease in coagulability of the blood, along with a decrease in glycolysis.

The tissue extracts and their place in the coagulation process have been thoroughly investigated by Mills.[46] The first attempts made at isolation of their thromboplastic elements were made by Wooldridge,[47] who found that the thromboplastic action of these extracts is due to a phospholipin, which, he determined, was a lecithin. In Howell's laboratory this was found to be cephalin (Mills). Mills [46] demonstrated that it is present in all organs but to a greater extent in the lung. He contended that, in addition to the phospholipoid material, the presence of the protein component of the tissue extracts is necessary for the manifestation of the maximum potency of the thromboplastic agents. The intravenous injection of phospholipin and the protein component of the tissues produces intravascular clotting and death.

43. Howell and Holt: Am. J. Physiol. **47:**328, 1919.

44. Howell: Am. J. Physiol. **71:**553 (Feb.) 1925; Bull. Johns Hopkins Hosp. **42:**199 (April) 1928.

45. Stuber and Lang: Biochem. Ztschr. **212:**16, 1929.

46. Mills: J. Biol. Chem. **40:**425 (Dec.) 1919.

47. Wooldridge, L. C.: On Chemistry of the Blood and Other Scientific Papers, London, Kegan Paul, Trench, Trübner & Co., 1893.

EXPERIMENTAL WORK

In selecting animals for this experimental work, it was decided that dogs would be most suitable. The biliary system of the dog is quite similar to that of man.

The greatest difficulty confronting one, in producing experimental obstructive jaundice in dogs, is the presence of accessory bile ducts. Occasionally, one or more hepatic ducts empty directly into the duodenum. Rarely, there is a duct from the gallbladder opening into the duodenum. It is necessary to interrupt every channel carrying bile from the liver in order to produce jaundice that will persist. There are so many branches joining the various bile ducts that the duct or ducts, overlooked at one operation, following which the jaundice subsides, are found at the time of the second operation to be enormously dilated. These enlarged channels apparently are sufficient to allow passage of the noxious bile to the duodenum. In the course of two or three days the stagnation is relieved and the jaundice disappears.

Dogs suffering with obstructive jaundice succumb within a relatively short period of time. Therefore, few of the observations are made in the presence of long-standing cholemia.

Twenty-seven animals were subjected to acute obstructive jaundice. The common bile duct and accessory ducts, when present, were divided between ligatures. On the third or fourth day each dog suffered with jaundice that could be recognized clinically. There was an icteric discoloration of the conjunctivae and skin. The feces became putty-colored or clay-colored and typically acholic, and biliuria was present. The dogs were perceptibly ill, and severe toxemia was evident.

Six of the dogs died before biliary obstruction had begun to produce a marked effect. One dog died on the operating table, as the result of pulmonary collapse. There was a diaphragmatic hernia on the right side, with the spleen, omentum and one lobe of the liver in the right pleural cavity. As this hernia was reduced, collapse of both lungs occurred. A rent was found in the mediastinal pleura, probably secondary to collapse of the right lung. Collapse of the left lung followed. Another animal died the day following operation. The cause of death was given as asthenia. Probably operative trauma played its part here, too, as the duct was located and ligated with considerable technical difficulty. Three dogs suffered evisceration and succumbed as the result of self-mutilation, followed by hemorrhage One died three days after operation, the cause of death undetermined. One dog with jaundice died on the eighth day; the cause of death was pneumonia.

Fifteen of the twenty-one animals that lived to show the effects of biliary obstruction died early, the average length of life being 15.7 days. Of the number (twenty-one) that survived to develop jaundice.

twenty-one (100 per cent) died of diffuse hepatitis, the average length of life being 31.6 days. The livers in gross, both on the surface and on section, showed areas of destruction, which were bile-stained. The peritoneum and all viscera were bile-stained.

Determinations of the fibrinogen in the blood plasma were made at intervals during the disease. The Wu method[48] was used. This method may be used with impunity, if one attempts to determine fibrinogen for comparative analysis, as was done in approaching this problem. The figure given by Wu for the tyrosine equivalent for the human being was 16.4. This was calculated on an average of only two determinations, 16 and 16.8, as given in the original publication. It may be realized that, even with the difference of 0.8 in these figures, there exists a considerable variation, and that the percentage of error is not to be overlooked. The tyrosine equivalent for dogs (17.1) was derived from an average of twenty-four normal determinations. There was considerable variation in the different figures that were determined, and an average of these was used. The percentage variation in the end-results was not greater than the percentage variation of the figures for the tyrosine equivalent. Thus the figure, as stated, should hold as a fair multiplicand in the calculation of the fibrinogen values for use on a comparative basis.[49]

In determining the tyrosine equivalent for the dog, twenty-four determinations were made. The values varied from 12.5 to 19.7, and the range of error is rather wide for one to consider using the method without reservation for exact determinations of the fibrinogen content of plasma. It may be added that, in making the last twelve determinations, great care was exercised, and on the filtrate from each specimen two determinations of both nitrogen and tyrosine were made as a check; it was found that the greatest variation in these figures was negligible when the final equivalent figure was calculated.

A table of the averages of the percentage increases in fibrinogen content of the plasma on successive days, with the number of animals on which determinations of this plasma component were made, is appended (table 1). The figure given represents the percentage increase above the normal for each dog.

An average was made of the fibrinogen determinations of each week. The percentage increase (above the average of the normal fibrinogen content for the twenty-seven dogs) for each week was calculated (table 2).

It is evident from the analysis of table 2 that there is a constant increase in the fibrinogen content of the plasma from week to week in

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48. Wu: *J. Biol. Chem.* **51**:33 (March) 1922.

49. Bliss, Sidney W.: Personal communication.

experimental obstructive jaundice. One must keep in mind, however, that relatively few determinations were made during the fourth week, for reasons that have been given.

The LaMotte-Pigford colorimetric method was used for determination of the icterus index.

The average of the determinations of the icterus index on the dogs before operation was 1.9 units. There was a gradual increase in the

TABLE 1.—*Average Percentage Increase of Fibrinogen in Plasma in Experimental Obstructive Jaundice*

Day	Percentage Increase	Number of Animals
3d	33	3
4th	16	8
5th	63	13
6th	60	4
7th	11	4
8th	27	10
9th	37	2
10th	66	3
11th	50	6
12th	69	1
13th	13	3
17th	12	1
18th	62	6
19th	38	1
20th	57	2
22d	72	1
24th	78	1
25th	58	1
29th	16	2
31st	74	2
32d	12	1
33d	52	1

TABLE 2.—*Average Weekly Percentage Increase of Fibrinogen in Plasma in Experimental Obstructive Jaundice*

Week	Percentage Increase	Number of Animals
1st	44	29
2d	46	29
3d	53	10
4th	62	4

average up to the eighth day. After the eighth day, there began a fluctuation that was not regular. The icterus index varied from 3 to 75 units after the initial increase. During the first, second, third, fourth and fifth weeks, the averages of the icterus indexes were 27, 28, 21, 17 and 35 units, respectively. Whereas the average for the first week was rather low, the highest figures of this determination were consistently noticed in the last two or three days of that week. The average for the fifth day was 26 units; for the sixth day, 32 units; for the seventh day, 52 units. There was a general decrease in the icterus

in the second week, but it was apparently more constant at this time, only varying from 20 to 36 units. During the third week, the icterus index approximated 20 units; during the fourth week, the average was 17 units, and during the fifth week, 35 units.

The coagulation time was estimated by means of the Brodie-Russell-Boggs coagulometer.

It was found that the average normal coagulation time of the twenty-seven dogs was 1 minute and 32 seconds. The coagulation time was
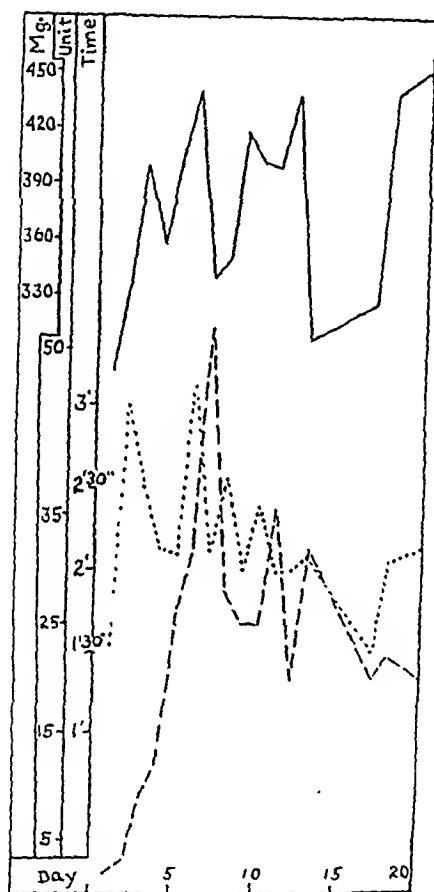

Fig. 1.—This and the graphs in figures 2, 3, 4 and 5 show the variations in fibrinogen content of the blood plasma, coagulation time and icterus index in experimental obstructive jaundice. The solid line represents the fibrinogen content of the plasma in milligrams; the dotted line, the coagulation time in minutes and seconds, and the broken line, the icterus index in units. In this graph are represented the daily averages of these determinations on all of the animals.

found to be consistently increased throughout the experiment, but not in a regular manner. However, the averages for the first, second, third, fourth and fifth weeks were 2 minutes and 35 seconds, 2 minutes and 10 seconds, 1 minute and 54 seconds and 2 minutes and 25 seconds, respectively.
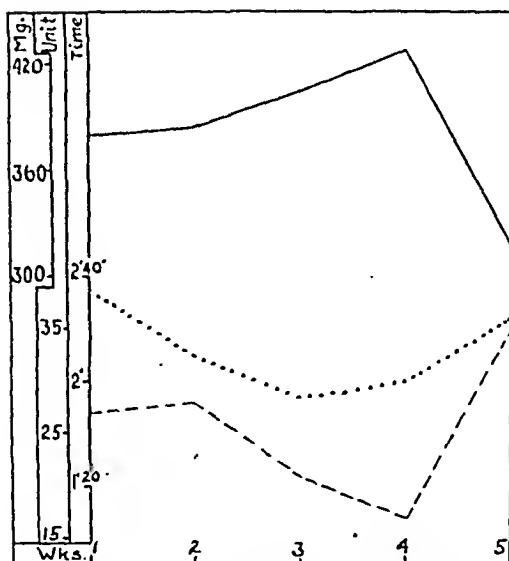
Fig. 2.—Weekly averages of the determinations of fibrinogen, coagulation time and icterus index of all the animals.
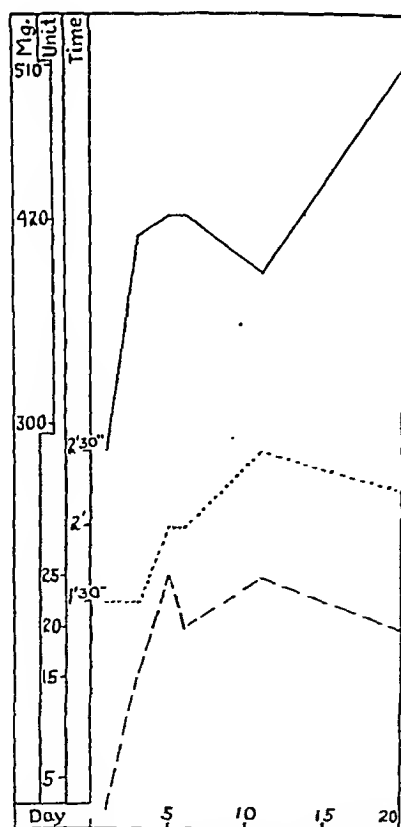

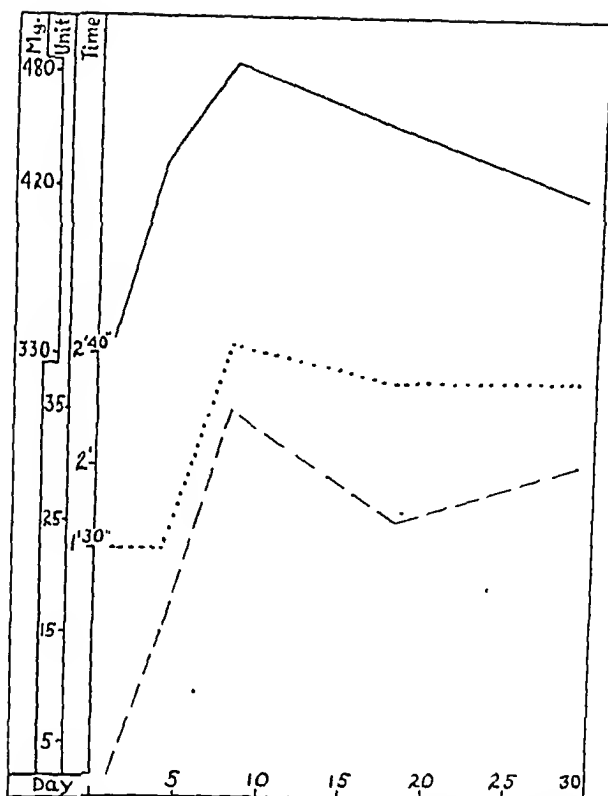Fig. 3.—Record of variations in the determinations for typical animal 1.

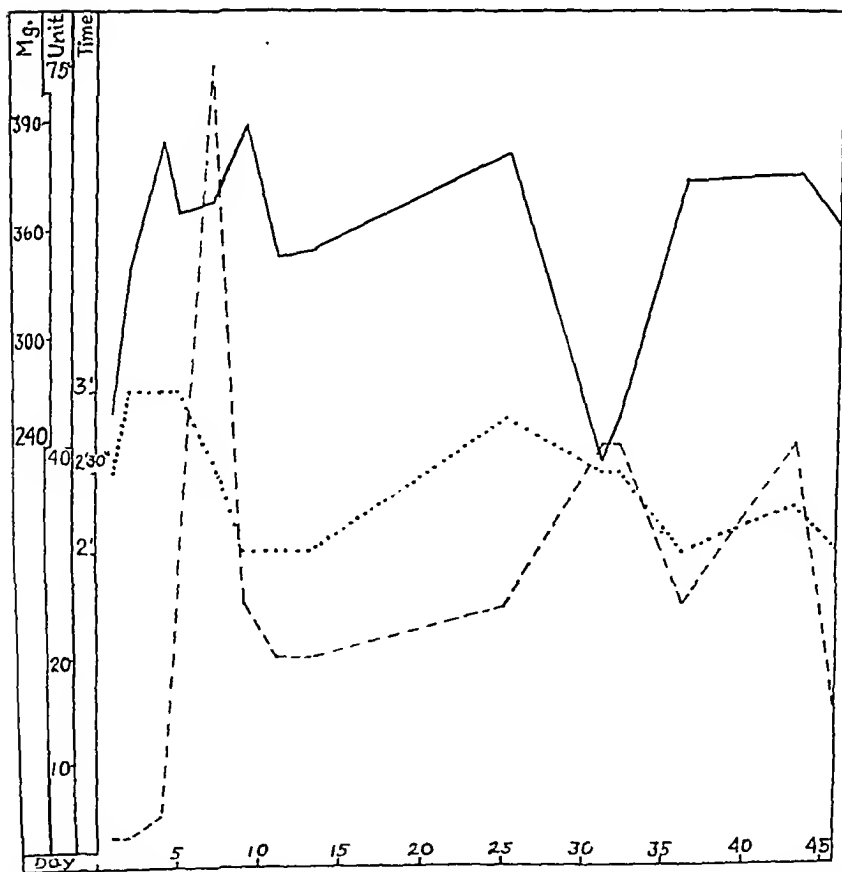Fig. 4.—Record of variations in the determinations for typical animal 2.

Fig. 5.—Record of variations in the determinations for the animal that survived the operation for the longest period.
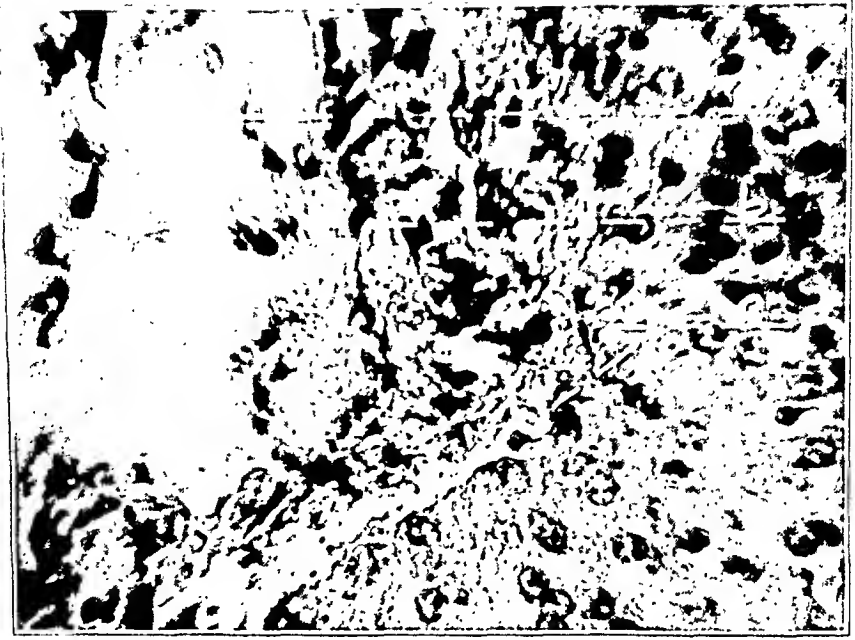
Fig. 6.—Damaged liver in experimental obstructive jaundice (under high power magnification), showing (*a*) hyalin-like material, (*b*) beginning cirrhosis and (*c*) hepatic necrosis at the periphery. The hepatic parenchyma in this slide was seen to be decidedly damaged.
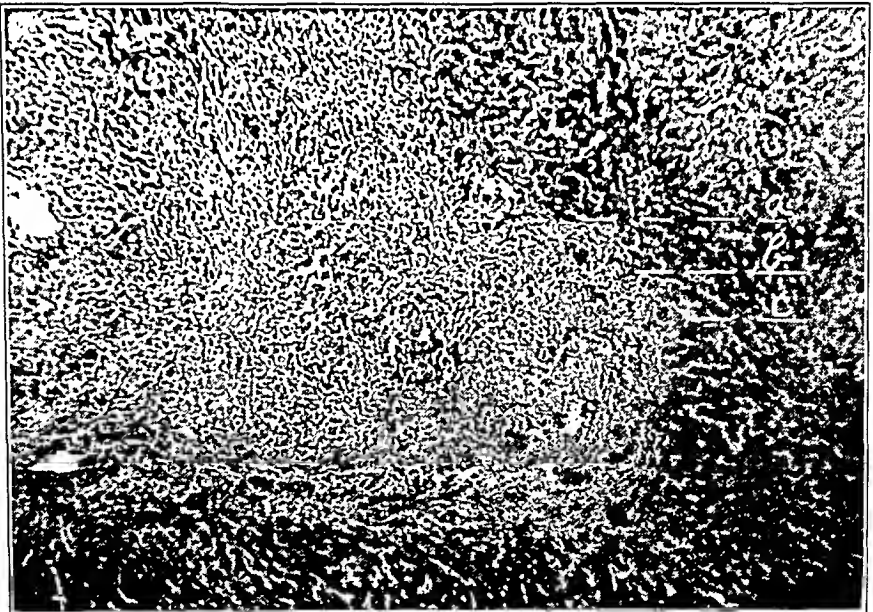

Fig. 7.—Damaged liver (low power) showing (*a*) fibrous connective tissue, (*b*) areas of hepatic cells undergoing degeneration and (*c*) cells of parenchyma unchanged. These areas, representing the third stage, are much larger than those in either of the two previous stages. The fibrous connective tissue has replaced the hyaline material, except for a few small areas.

PATHOLOGY

As has been stated, the primary cause of death of most of the animals could be attributed only to hepatic degeneration. The livers presented areas of destruction, which were apparent on the surface and on gross section, and which were bile-stained. These areas varied in diameter from 1 mm. to 3 or 4 cm.

The microscopic sections of the livers of the animals that had suffered from the mildest degree of jaundice showed a definitely disarranged hepatic parenchyma in the lobules, but a very small degree of destruction of the cells per se.

Fig. 8.—Damaged liver (high power) showing (*a*) fibroblasts and (*b*) hyaline material. There is seen complete replacement of hepatic parenchyma, and only a few areas of hyaline material remain.

A further lesion, which may be divided into three stages, was observed. These consisted of: 1. Small areas of necrosis, which were infiltrated by leukocytes, the lymphocyte being the predominating cell; polymorphonuclear leukocytes were only occasionally observed. These areas studded the parenchyma throughout, and because of the types of cells found were classified as subacute inflammatory processes. 2. Larger areas than these, including the same cellular elements but, in addition, a hyalin-like material, which predominated (fig. 6). 3. Areas, even larger than those classified under 2, in which cirrhosis was observed, a proliferation of fibrous connective tissue (figs. 7 and 8).

Fig. 9.—Damaged liver (low power) showing (a) central vein of lobule, (b) hepatic necrosis, (c) areas of fatty degeneration and (d) normal hepatic cells at periphery of lobule. In this photomicrograph are represented areas of central necrosis in the lobule. The cells at the periphery are unaffected. This shows the changes that took place in the livers of most of the animals.
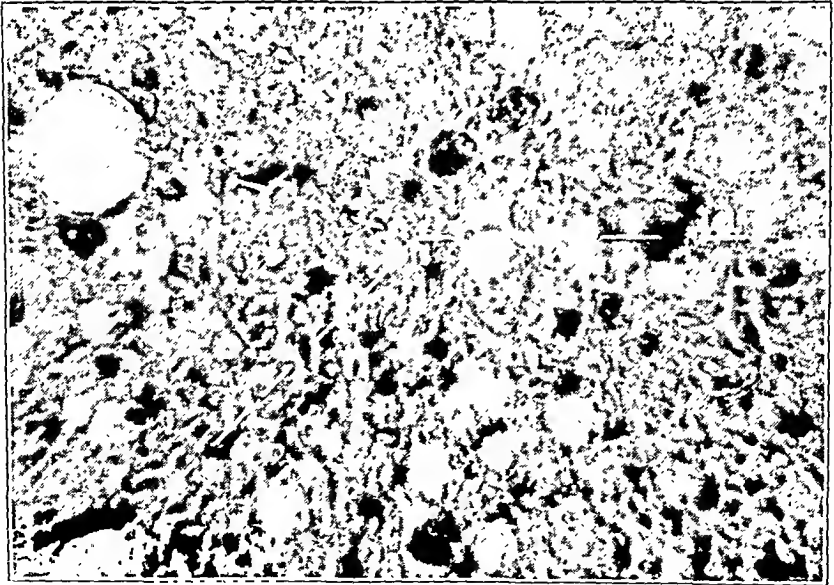

Fig. 10.—Areas of fatty degeneration (a) under high power magnification.

Central necrosis of the lobules was present in the greatest number of the animals. This lesion consisted of fatty degeneration (figs. 9 and 10). It was more pronounced in the central part of the lobule for two reasons: first, because the cells in the center of the lobule were the more constantly bathed by the bile, and second, because their blood supply was directly affected owing to injury to the hepatic vessels. The cells at the periphery were unchanged owing to the unimpaired blood supply, the result of an intact portal system and because the bile could be transported more readily from this area for the same reason.

<center>COMMENT</center>

It is evident from the results obtained that no parallelism exists between the fibrinogen content of the blood and the degree of icterus. However, the fibrinogen content of the plasma was high in the first week following obstruction of the extrahepatic bile ducts. The icterus index and coagulation time were also increased during the first week. The fibrinogen content continued to increase during the second and third weeks, whereas the icterus index and coagulation time either decreased or remained stationary. The results obtained during the fourth and fifth weeks are not dependable, because of the fact that comparatively few determinations were made during this stage of the condition.

The increase in the fibrinogen content and the coagulation time during the first week might be considered as the result of the operation, but it is evident that the greatest percentage increase above normal occurred on the fifth day. It seems reasonable that after the first day or so the effect of the operation can be dismissed as a factor in causing this increase. Hueck[50] observed that the fibrinogen content of the plasma was increased after operation.

The results of this experiment have shown that bile is an irritant to the liver and in obstructive jaundice is a stimulus to the formation of more fibrinogen by the liver as is acute inflammation, thus corroborating the results of Wiener and Wiener. It is agreed that this is probably also due to the increase in the permeability of the hepatic endothelium.

It is found that the fibrinogen content of the blood increased considerably just before death, which might be attributed to concentration of the plasma by dehydration.

The fluctuation of the coagulation time is found to coincide with that of the degree of icterus. This was observed in a great majority of the individual animals (figs. 1 and 2). The increase in the icterus indexes is self-explanatory. Following the obstruction in the

50. Hueck: Arch. f. klin. Chir. **136:**627 (Aug.) 1925.

biliary system the normal exit for the bile was blocked. One is justified in assuming that the reason the icterus decreased after the first week was that a diminution in the amount of bile produced by the liver had occurred, owing to destruction of liver cells.

SUMMARY AND CONCLUSIONS

An attempt has been made to determine whether or not some relationship exists between the fibrinogen content of the plasma, the degree of icterus and the coagulation time of the blood in obstructive jaundice. If some definite relationship exists among these factors, it is reasonable to suppose that it would be enlightening as to the cause of hemorrhage in the presence of jaundice.

It must be stated that as yet there is no adequate proof that any one factor is responsible for this hemorrhage.

Deficiency of calcium in the serum should not be considered as a causative factor in the production of hemorrhage in obstructive jaundice. The results of investigations reported in the literature indicate that a deficiency of calcium is not constant in jaundice, nor is it directly implicated in prolonging the coagulation time.

The contention favoring heparin as a cause for this bleeding is not substantiated by clinical or experimental proof. Little is known of the presence of heparin in the blood, and one can only theorize as to what factors influence the fluctuation of the quantity of heparin present in the circulating blood. The present investigation demonstrates that bile causes destruction of hepatic parenchyma, and the possibility that heparin is increased in the blood in obstructive jaundice is admitted.

It is concluded from this experimental work that the fibrinogen content of the plasma is not decreased in experimental obstructive jaundice. Therefore, hemorrhage in the presence of jaundice is not due to a deficiency of this component of the plasma.

The fibrinogen content of the plasma is increased in acute obstructive jaundice, probably owing to the irritative effect of the bile on the liver.

The coagulation time remained above normal limits in practically all of the determinations, but it did not parallel the fibrinogen content of the plasma. Corroborating the opinion of Ravdin, Riegel and Morrison [25] and Bancroft, Kugelmass and Stanley-Brown,[26] it is concluded that the coagulation time is not a satisfactory index of a hemorrhagic tendency in the presence of jaundice.

The contention of Peters and Van Slyke [8] that a decrease in fibrinogen content of the plasma does not parallel the degree of destruction of the liver is corroborated. It was found that generally an increase in fibrinogen content parallels the extent of damage to the liver.

ROENTGENOLOGY OF EXPERIMENTAL MESENTERIC VASCULAR OCCLUSION

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Mesenteric vascular occlusion still remains one of the most difficult surgical problems. The difficulty in arriving at an early diagnosis undoubtedly accounts for the high mortality, quoted by various writers as being about 70 per cent. The delay in diagnosis is often unavoidable owing to a lack of definite symptoms, even though the damage to the intestinal tract is severe. The same difficulty is experienced in the early clinical diagnosis of simple intestinal obstruction. The effects on the physiology of the bowel of early mesenteric thrombosis or embolism may be compared in some respects with those of simple intestinal obstruction, as well as those of the strangulation type. These conditions result in stasis of the intestinal contents, decrease in the absorption of gas and fluid by the intestinal wall, excretion of fluid into the lumen of the bowel proximal to the affected segment and intestinal hemorrhage and infarction of the involved segment. Although it is an established fact that the roentgen findings of gas and fluid levels in the small intestine have greatly enhanced the diagnosis of simple intestinal obstruction,[1] attention has not been directed to the fact that a similar roentgen picture is produced in mesenteric vascular occlusion.

The object of this paper is to report roentgen studies of experimental occlusion of the mesenteric vessels. The lesions produced in the experimental animals were made to resemble as closely as possible those found in patients.

PATHOLOGY

In the thirty-six cases reported by Larson,[2] 39 per cent of the vascular occlusions were found to be arterial at autopsy, 44 per cent venous and 17 per cent a combination of the two.

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1. Swenson, P. C., and Hibbard, J. S.: Roentgenographic Manifestations of Intestinal Obstruction, Arch. Surg. **25**:578 (Sept.) 1932.

2. Larson, L. M.: Mesenteric Vascular Occlusion, Surg., Gynec. & Obst. **53**: 54 (July) 1931.

Klein [3] said that the two types of occlusion are about equally divided. He expressed the belief that arterial occlusion may be caused by either thrombosis or embolism. The etiology of the arterial emboli, which, he stated, include about 2 per cent of cases, must arise in the left side of the heart either from vegetations on the valves or from thrombi in the auricles, as was found in five cases in Larson's series. The arterial thromboses are generally associated with arteriosclerosis, although at times they may be due to pressure of an aortic aneurysm on the artery or to extension of a clot from an aneurysm into the mouth of the artery.

Klein further stated that occlusion of the vein is practically always caused by thrombosis, although some cases are reported in which the etiology is unknown, and others in which only a remote focus of infection exists as a possible cause. The most common cause of venous occlusion is a thrombophlebitis resulting from either acute appendicitis or a pelvic inflammatory condition.

The first effect on the involved segment of intestine of a sudden closure of the superior mesenteric artery, according to most observers, is violent tetanic contractions associated with marked anemia. This condition lasts from two to three hours and is followed by a relaxation and congestion and finally by hemorrhagic infarction. The observations to be reported do not exactly agree with this view. The sequence of events in our experiments was different.

The preliminary contractions were noticed, but numerous subserous hemorrhages varying from 0.25 to 1.5 cm. in diameter resulted within fifteen minutes, and a generalized mild congestion, dilatation and an absence of peristalsis occurred within thirty minutes. This condition was not changed to a great extent at the time the animals were killed, four and six hours later. These phenomena apparently account for the early presence of gas and fluid levels seen in the involved segments on the roentgen film.

Klein stated that all experimenters agree that ligation of the superior mesenteric vein leads constantly to hemorrhagic infarction. He pointed out that in patients the result may be different because it is known that thrombophlebitis generally causes a gradual occlusion. Nevertheless, numerous cases are reported by Larson and others in which an infarcted, congested and soggy segment with dilatation of the proximal intestine was found at operation. These cases would indicate that, although more time is consumed in the process of occlusion, the ultimate outcome is similar to the experimental venous ligations. In the animals of this series, in which the veins to a segment of intestine were ligated, a marked

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3. Klein, S.: Embolism and Thrombosis of Mesenteric Artery, Surg., Gynec. & Obst. **33**:385 (Oct.) 1921.

engorgement and a mild contraction immediately occurred, but no relaxation or dilatation followed during the time the abdomen was open. Further, no gas shadows or fluid levels were observed in the involved segment on the roentgen film up to the time the animals were killed, six hours later.

Ligation of both the arteries and the veins of a segment of gut produced the same objective signs that were noted following arterial occlusion, except for the fact that a more marked and rapid congestion and discoloration occurred.

Experimental studies and clinical observations indicate that mesenteric arterial or venous occlusion, severe enough to cause infarction in a segment of intestine, will later cause dilatation of the proximal intestine and result in abdominal distention. These dilated loops of bowel with their fluid levels distributed diffusely over the abdomen will show on the roentgen film.

EXPERIMENTAL DATA

Three groups of dogs were studied in this series of experiments (table). All of the animals were operated on under ether narcosis and with strictly sterile technic. As soon as gas shadows and fluid levels could be demonstrated on the roentgen films, the abdomen was again opened under ether anesthesia, and the condition of the intestine was observed.

In group A, dog 1, the superior mesenteric artery was ligated just distal to the origin of the inferior pancreaticoduodenal artery. In dog 2, the trunk of the superior mesenteric artery was approached through a retroperitoneal route and ligated about 5 cm. distal to its junction with the aorta. Roentgen films of these two animals diselosed gas shadows, and fluid levels were found on the roentgen film early and simultaneously, i. e., at one and one-half and four hours, respectively. At postmortem examination there were numerous areas of discoloration and a mild dilatation.

Four procedures were done in group B. In dog 1, the portal vein was ligated 6 cm. from its entrance into the liver. In dog 2, the tributaries of the superior mesenteric vein from the jejunum, ileum and eeeum were ligated. In dog 3, one half of the jejunum and all of the ileum, and in dog 4, about 12 cm. of the lower ileum were included in the occlusion.

In dogs 1, 2 and 3 of this group no roentgen findings were elieited. When the abdomens were opened six and eight hours later, the entire small intestine and its mesentery were found to be mildly edematous and bluish purple, and the lumen of the intestine was filled with blood. The intestine was not dilated. The negative roentgen findings were probably caused by the fact that the extensive hemorrhage into the lumen of the

bowel displaced the gas. Dog 4 showed no effects from the ligation, since the collateral circulation through the longitudinal branches of the anastomosis apparently was adequate. The animal recovered.

Since the negative results in the first two dogs of the foregoing group were probably due to the filling of the intestinal lumen by blood, two more animals were studied in group B. Our object was to produce a definite

Results of Experiments

Experimental Animal	Presence of Gas	Presence of Fluid Levels	Vessels Occluded	Condition of Involved Segment
Group A				
1	4 hours	4 hours	Superior mesenteric artery to ileum and jejunum	Slightly dilated; many subserous hemorrhages; gross color: slightly darkened
2	1½ hours	1½ hours	Superior mesenteric artery to ileum and jejunum	Moderately dilated; many subserous hemorrhages; gross color: slightly darkened
Group B				
1	3½ hours disappeared at 5½ hours	None	Portal vein	Engorged and soggy; bluish red
2	1 hour disappeared at 3 hours	None	Superior mesenteric vein involving jejunum, ileum and proximal colon	Engorged and soggy; bluish red
3	None	None	Superior mesenteric vein involving half of jejunum and ileum	Engorged and soggy; contracted; appendix contained gas and fluid; bluish black
4	None	None	Superior mesenteric vein involving half of ileum	Animal recovered
5	3 hours	5 hours	Superior mesenteric vein involving 10 cm. of ileum	Severe hemorrhage; engorged, edematous and contracted in areas
6	3 hours	5 hours	Superior mesenteric vein involving 10 cm. of ileum	Severe hemorrhage; engorged, edematous and contracted in areas; proximal bowel dilated and contained gas and fluid
Group C				
1	2 hours	6 hours	Superior mesenteric artery and vein to 40 cm. of ileum	4 cm. of ileum engorged and soggy; bluish black; proximal gut slightly dilated
2	2 hours	5 hours	Superior mesenteric artery and vein to 12 cm. of ileum	4 cm. of ileum engorged and soggy; bluish black; proximal gut slightly dilated
3	2 hours	4 hours	Superior mesenteric artery and vein to 12 cm. of ileum	4 cm. of ileum engorged and soggy; bluish black; proximal gut slightly dilated; at 20 hours perforation had occurred; all other cases autopsies at 6 hours

venous occlusion in a relatively short segment of bowel in the lower ileum. This was accomplished by ligating the mesenteric veins from 10 or 12 cm. of lower ileum and by placing a suture through the mesenteric border of the intestine down through the submucosa, thus obliterating the longitudinal anastomosing branches. This procedure was quite successful in producing a venous occlusion in a small segment of gut. At postmortem examination, the involved segment and its mesentery
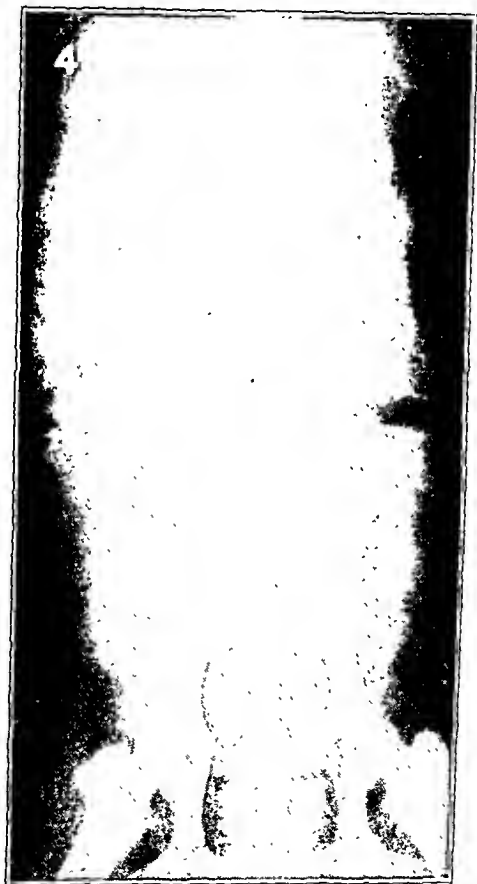

Fig. 1.—Film of the abdomen of a dog in the erect position, in which the superior mesenteric artery has been blocked as described in the text. Note the gas shadows and fluid levels, which appeared simultaneously at four hours.

were found to be markedly edematous, hemorrhagic and slightly contracted, and the lumen of the segment and the distal bowel were filled with blood. The proximal intestine was moderately dilated, and gas shadows and fluid levels were found on the roentgen film in three hours and five hours, respectively (fig. 2).

In group C, both the veins and the arteries were occluded in three animals. In dog 1, the mesenteric arteries and veins were ligated to a
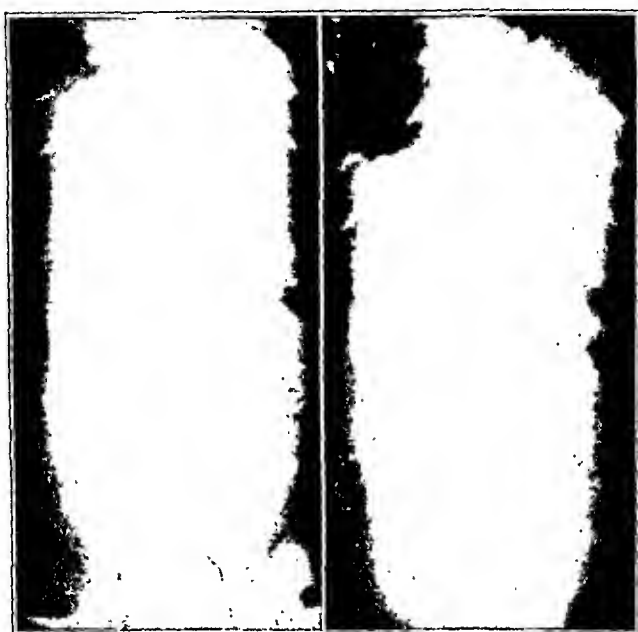
Fig. 2.—Films of the abdomen of a dog in which the tributaries of the superior mesenteric vein, including 12 cm. of the ileum, have been occluded. Note the gas shadows and fluid levels at two and five hours.
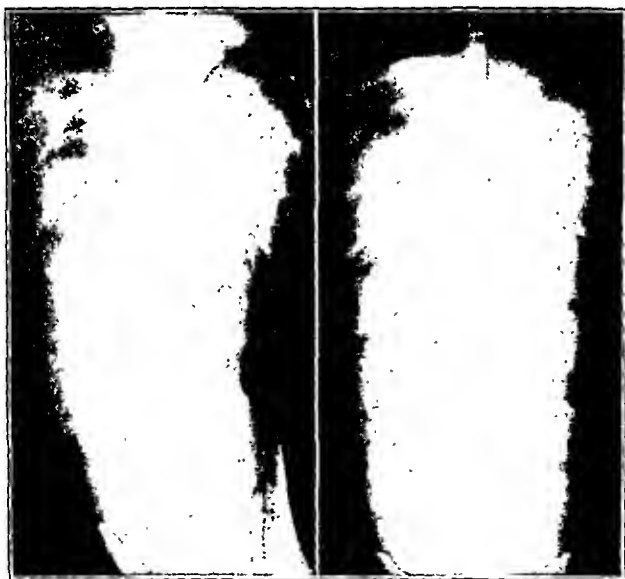

Fig. 3.—Films of the abdomen of a dog in which the superior mesenteric arterial branches and venous tributaries have been occluded through 12 cm. of the ileum. Note the gas shadows at two hours and the fluid levels at four and a half hours.

segment of lower ileum about 40 cm. in length, and in dogs 2 and 3, the occlusions involved about 12 cm. of the lower ileum. The roentgen films disclosed gas shadows in two hours and fluid levels in from four to six hours in all animals (fig. 3).

COMMENT

This experimental study indicates that it is possible very early to elicit roentgen signs of intestinal obstruction following mesenteric vascular occlusion.

These signs are indistinguishable from those found in mechanical obstruction. Thus, the differential diagnosis from simple mechanical obstruction cannot be made, of course, on the roentgen findings alone, but involves a careful consideration of the accompanying clinical evidence, particularly as to the existence of possible causes of either condition. On the other hand, the important fact remains that the roentgen evidence of intestinal obstruction appears before abdominal distention can be detected and before damage to the involved segment has become too severe. Except in the cases of extensive venous block in which the damage perhaps is too great in any event for surgical relief, the roentgen examination may be a definite aid in reaching a decision to operate.

SUMMARY

Roentgen examination after experimental occlusion of the mesenteric arteries and veins disclosed gas and fluid levels in dilated loops of small intestine in from two to six hours, which are indistinguishable from those following mechanical intestinal obstruction. However, this evidence should be of aid in early diagnosis and in making an early decision to intervene surgically.

ESTABLISHMENT OF CIRCULATION IN TUBED SKIN FLAPS

AN EXPERIMENTAL STUDY

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The assurance of the circulation of pedunculated skin flaps [1] is of vast importance in plastic surgery. Often it is possible to form a single pedicled flap and to shift it into its new bed immediately. When this is done one must remember that roughly the length of the flap should not be more than two and a half times the width of the pedicle, unless the flap contains an artery, such as the anterior temporal, in which case it may be as long as the artery will nourish and the pedicle may be very narrow, consisting in fact, if necessary, of only the artery and accompanying veins. Frequently much longer flaps are needed than those that can be conveniently made two and a half times the length of the pedicle, and these must often be obtained from an area in which no definite artery is available.

Flaps that are much more than two and a half times as long as the width of the pedicle may be developed by the delayed transfer method. By delayed transfer we mean that in order to assure its circulation a period of time is allowed to elapse between the raising of the flap and its transference to its its new bed. The best type of flap for the delayed transfer is the doubled pedicled flap, and a very satisfactory double pedicled type is that known as the tubed flap, which was developed during the world war by Gillies of London.

The main advantage of the tubed flap, besides its flexibility, is that it is a doubled pedicled flap the circulation of which is assured by the delay in transfer.

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1. A skin flap is made up of the whole thickness of the skin with as much of the subcutaneous tissue as is required. It is usually attached at some portion of its periphery by a pedicle, or pedicles, through which it receives its primary blood supply. A skin graft, on the other hand, is a free transplant whose blood supply is entirely derived from the tissue on which it is transplanted.

The question often arises as to the safest time to sever the pedicles of delayed transfer flaps. In other words, when will the circulation of such flaps be sufficiently developed to allow the division of the first pedicle, so that the circulation from the other will be adequate to nourish the flap without loss of tissue.

It is advised by different authors that from several weeks to as many months should be allowed to elapse before dividing one pedicle and making the transfer, but we have felt that in the majority of instances this long delay, while never disadvantageous as far as circulation is concerned, is actually unnecessary. We have allowed some of these flaps to stay as formed for as long as a year and half before dividing one pedicle and then transferring to its new bed. For the purpose of finding out how soon the circulation of a tubed flap adjusted itself and consequently how soon it was safe to divide the pedicle and transfer the flap, we undertook the following series of experiments in the hope that sufficient information might be obtained to be clinically useful.

EXPERIMENTAL STUDY

The development of an adequate blood supply in tubed skin flaps is of paramount importance in the utilization of this type of flap. Before the flap can be implanted in a new location, its blood supply from a single pedicle must be sufficient to nourish the entire flap. This necessitates not only an increase in the size or number of the blood vessels, but also a rearrangement of the vessels, corresponding to the long axis of the flap. The present study was undertaken in an attempt to follow, in chronological order, these changes occurring in the vascular bed.

Investigators, in the past, have concerned themselves chiefly with the development of the blood supply of free skin grafts. The development of the blood supply of whole thickness skin grafts has been worked out and the literature reviewed by Davis and Traut.[2] The effect of variations of orientation of skin grafts, in relation to the axis of their original blood supply has been studied by Paterno.[3] Square full thickness grafts were cut and replaced in their original bed. The control grafts were replaced without changing the orientation of their margins and showed 100 per cent survival with reestablishment of circulation after the second day. Grafts rotated 180 degrees with respect to their original orientation survived completely in 80 per cent and partially in 20 per cent of the cases, with reestablishment of circulation

2. Davis, J. S., and Traut, H. F.: Origin and Development of Blood Supply of Whole Thickness Skin Grafts, Ann. Surg. **82**:871, 1925.

3. Paterno, A.: Influenza della variazione di orientamento del lembo sullo attecchimento e sul ripristino dell circulo sanguino nei trapianti libri autoplastici di cute interna, Ann. ital. di chir. **4**:923, 1925.

retarded until after the fourth day. Grafts rotated 90 degrees from their original position survived completely in 66 per cent of the cases, partially in 20 per cent and failed to survive in 14 per cent. Their circulation was retarded until after the fourth day. These results suggest that the establishment of circulation in skin grafts is partially dependent on the orientation of the vessels of the graft in relation to those of the surrounding structures.

METHODS

In the attempt to study the establishment of a new circulation in tubed flaps, three methods were followed. The first was the determination of the size, number and arrangement of the blood vessels in cleared specimens, removed at intervals of from one to fourteen days following the construction of the tubed flaps. The second method was similar to the first except that an opaque material was injected into the flaps and the studies carried out on roentgenograms of the flaps. The third was a histologic study of the flaps of various ages.

Dogs were used throughout the experiments. The skin of the abdomen was shaved and prepared with iodine and alcohol. With the dogs under ether anesthesia, two double pedicled tubed flaps were outlined, one on either side of the abdominal wall with the long axis of the flap parallel to the long axis of the abdomen. The flaps were 8 to 10 cm. in length and 3 to 3.5 cm. in width, with their bases slightly flared, and were undercut in a manner to include a thin layer of subcutaneous tissue. The edges of the flaps were approximated with interrupted silk sutures, transforming the flaps into tubes with the epithelial surface outside, attached to the abdominal wall at each end in the form of a "valise handle." The skin defect beneath the tubed flap was closed by approximating the opposing skin edges with interrupted silk sutures. Sterile dressings were applied and kept in place for seven days. Usually, healing took place by first intention.

In the first series of experiments, the tubed flaps were separated from the abdominal wall at one end and the animal was given an intravenous injection of from 5 to 10 cc. of 1 per cent solution of toluidine blue, this quantity being sufficient to impart a definite blue color to the skin and mucous membranes. When the blue dye was seen coming from the cut end of the flap, the remaining attachment of the flap to the abdominal wall was cut and the specimen was fixed and cleared, the method [4] of Spalteholz [5] being used. The cleared flaps were then opened along the suture line, spread out flat and mounted in methyl salicylate.

In the second series, the animals were killed, the tubed flaps were separated from the abdominal wall at one end and the injection was made though the aorta. A suspension of barium in gelatin was used as the injection medium.[6] The injection was continued until the barium mixture appeared at the cut end of the flaps. The other pedicle of the flap was then divided, and roentgenograms were taken without opening the flaps.

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4. Fix in formaldehyde; bleach with hydrogen dioxide; wash in water twenty-four hours; dehydrate by passing through alcohols from 50 per cent to absolute; place in benzene (two changes); mount in methyl salicylate, U. S. P., 5 parts and benzyl benzoate 3 parts.

5. Spalteholz, W.: Ueber das Durchsichtigmachen von menschlichen und tierschen Präparaten, ed. 2, Leipzig, S. Hirzel. 1914.

6. Barium sulphate 1,000 Gm., powdered gelatin 300 Gm., distilled water 1,700 cc.

In both the first and second series of experiments, the entrance of the injection material into the flap was through a single pedicle, the upper pedicle being divided on one side and the lower pedicle on the other. This method was selected because the clinical utilization of pedunculated flaps necessitates the development of an adequate blood supply from a single pedicle before the flap can be implanted in a new location. The vessels demonstrated by the injection methods therefore represent the circulation which may be supplied by a single pedicle.

The third series of experiments made use of the flaps of the first series into which toluidine blue was injected. Sections were taken through the central portion of the flaps and stained with hematoxylin and eosin.
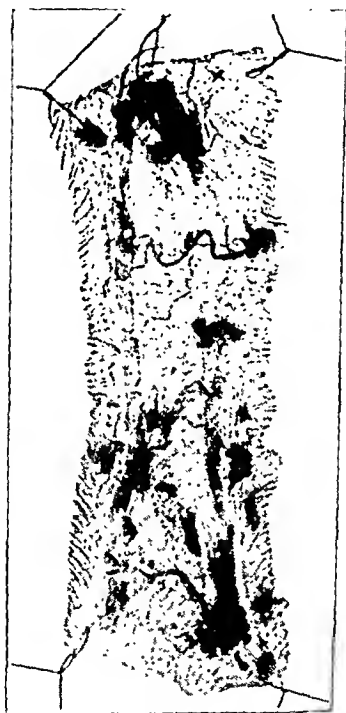

Fig. 1.—Typical opened, cleared specimen into which toluidine blue was injected and the flap removed immediately after its construction. Note the blood filled vessels crossing the flap at right angles to its long axis. Only the vessels immediately adjacent to the pedicle showed evidence of containing toluidine blue. Note that there were no vessels running parallel to the long axis of the flap.

RESULTS

With these three methods of study, the results may be summarized as follows:

Tubed flaps, removed immediately after their preparation showed blood-filled vessels crossing the flaps at right angles to their long axis. Only the vessels immediately adjacent to the pedicle showed evidence of toluidine blue within their lumen. There were no vessels running parallel to the long axis of the flaps.

Flaps removed at the end of one day showed a few vessels, filled with the injection mediums running almost the entire length of the flap. These vessels were more numerous at the region of the base of the flap, but there was a definite tendency for the long axis of the vessels to be parallel to the long axis of the flap.

At the end of four days, vessels containing the injection medium and running parallel to the long axis of the flap, were more marked.

Specimens removed on the seventh day showed what appeared to be a well developed blood supply, with vessels running from one end of the flap to the other.
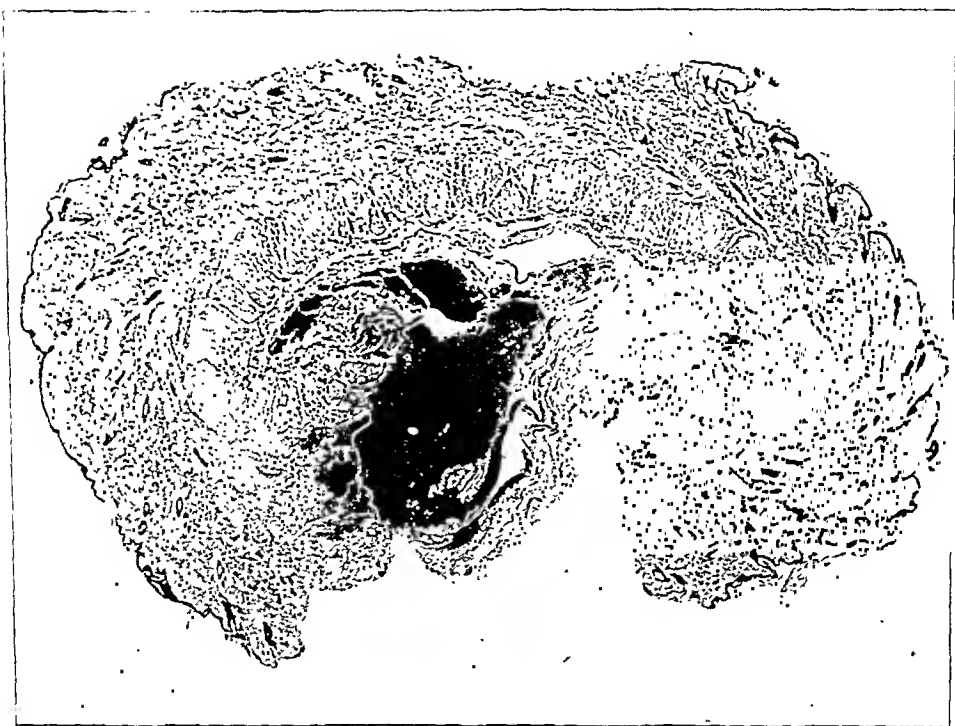

Fig. 2.—Photomicrograph of a section taken through the center of a flap removed immediately after its construction. There are a moderate number of small and medium-sized blood vessels. There is marked hemorrhage in the center of the tubed flap with slight extravasation of blood into the subcutaneous tissue.

From the seventh to the fourteenth day there appeared to be little change in the number, character or size of the vessels.

The microscopic study of sections taken through the central portion of flaps of different ages may be summarized as follows:

On the day of operation there were a moderate number of small and medium-sized blood vessels and marked hemorrhage in the center of the tubed flap with slight extravasation of blood into the subcutaneous tissue.

On the first day a moderate number of small and medium-sized blood vessels were seen with diffuse extravasation of blood throughout the subcutaneous tissue and slight polymorphonuclear leukocytic infiltration.

On the fourth day there were small and medium-sized blood vessels, apparently more in number than on the first day, marked polymorphonuclear leukocytic infiltration in the cutis vera.

On the seventh day there were many small, medium and large blood vessels in the subcutaneous tissue and in the deeper portion of the cutis
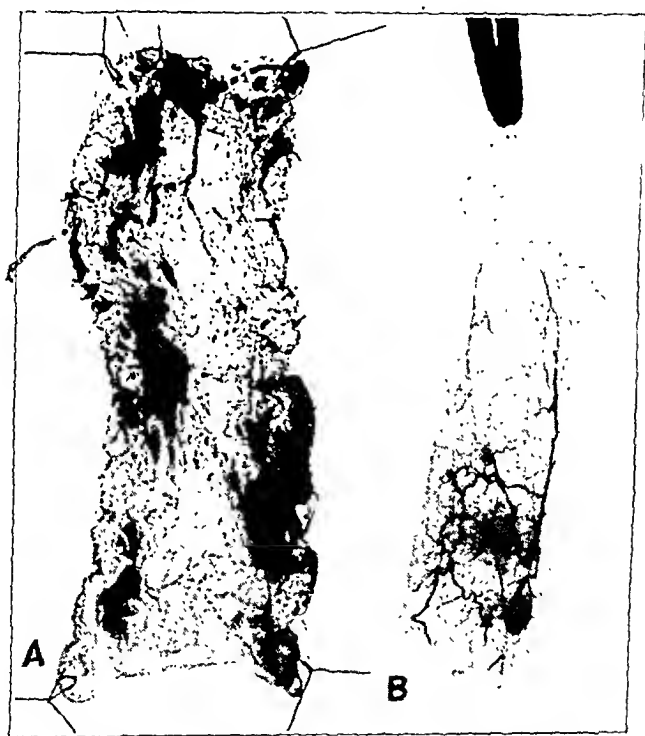

Fig. 3.—*A*, typical opened, cleared specimen into which toluidine blue was injected and the flap removed after twenty-four hours. *B*, roentgenogram of a flap into which an opaque mixture was injected and the flap removed after twenty-four hours. A few vessels filled with injection material can be seen running almost the entire length of the flap. These vessels are more numerous at the region of the base, but there is already a definite tendency for the long axis of the vessels to be parallel to the long axis of the flap.

vera, and early granulation tissue in the cutis vera, containing many capillaries.

On the eleventh day many small, medium and large blood vessels were seen in the subcutaneous tissue and in the cutis vera; there was well developed granulation tissue in the cutis vera.

SUMMARY OF EXPERIMENTS

Injection experiments of tubed double pedicled skin flaps indicate the establishment of an adequate blood supply from a single pedicle within seven days. Histologic studies of these specimens support this conclusion.

The development of an adequate blood supply appears to be dependent on three factors: (1) an increase in the size of the vessels; (2) an increase in the number of functioning vessels, and (3) a reorientation of the main vascular channels corresponding to the long axis of the flap.

Fig. 4.—Types of roentgenograms of flaps into which an opaque mixture was injected and the flaps removed at the end of four days. The vessels containing the injection medium and running parallel to the long axis of the flap are more marked than in the one day specimens as shown in figure 3.

CLINICAL APPLICATION

In order to understand the clinical problem with which we are dealing, it may be advantageous to review the anatomy of the blood supply of the human skin.

The anatomy of the cutaneous blood vessels in man has been carefully described and illustrated by Spalteholz.[7] There is a marked

7. Spalteholz, W.: Die Verteilung der Blutgefässe in der Haut, Arch. f. Anat. u. Entwcklngsgesch., 1893, pp. 1-54.

variation in the number and size of the vessels to the skin in different regions of the body. The number is greater to those portions of the skin which are subjected to external pressure, such as the palms of the hands, soles of the feet and the gluteal region.

All branches of the arteries supplying the skin anastomose freely with each other and with neighboring vessels and form a cutaneous arterial network situated in the deepest layer of the cutis. The mesh of this network is smaller in the more vascular regions. From this, arched and branching vessels proceed outward, and anastomosing, form
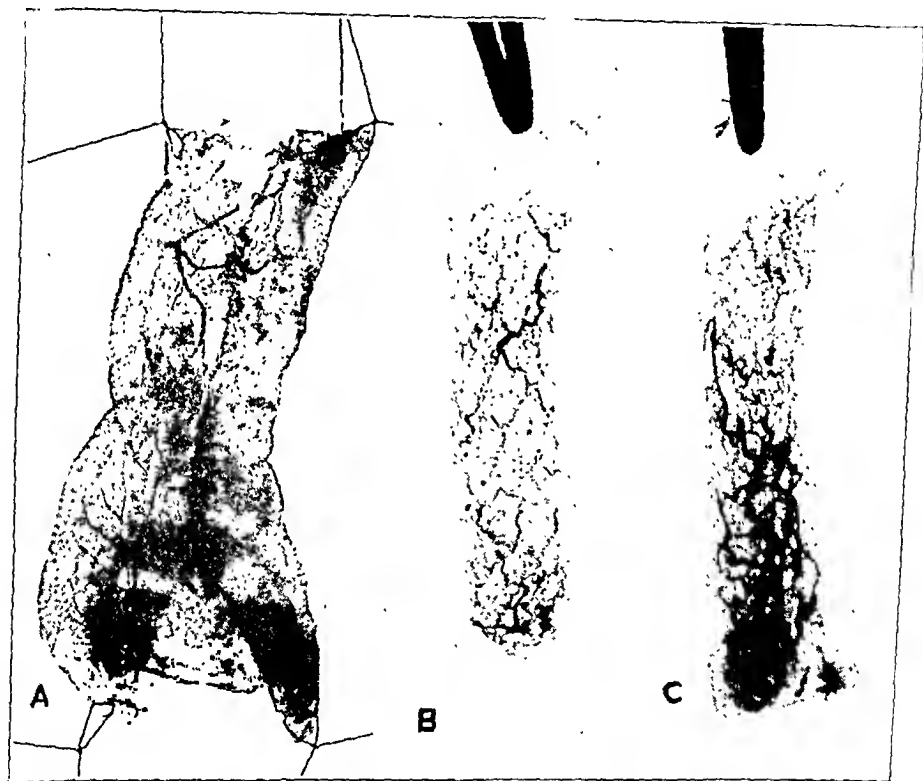

Fig. 5.—*A*, cleared specimen into which toluidine blue was injected and the flap removed at the end of seven days. Compare this with the vessels shown in figures 1 and 3 *A* and note the vessels running the full length of the flap. *B* and *C*, roentgenograms of flaps into which an opaque mixture was injected and removal done at the end of seven days. These specimens show a well developed blood supply with numerous vessels running from one end of the flap to the other. Compare these with figures 3 and 4 and note the marked change in the size and number of the vessels and in the reorientation which has occurred.

a second subpapillary arterial network near the junction of the middle and outer thirds of the cutis.

Numerous small branches arise from the subpapillary network and run as terminal arterioles to the superficial layers of the skin. Most of these turn and course for a short distance parallel to the surface of

the skin, following, in the palm of the hand and the sole of the foot, the direction of the papillary ridges beneath which they run. They send their twigs to the arterial limbs of the capillary loops, lying in the papillae.

The venous blood, returning from the capillary loops in the papillae, passes through several networks. The first lies immediately beneath the bases of the papillae and receives blood from the venous limbs of the capillary loops and from minute collecting venules formed by the union of several such capillaries. Almost immediately beneath this is a second venous network, the two intercommunicating freely by short
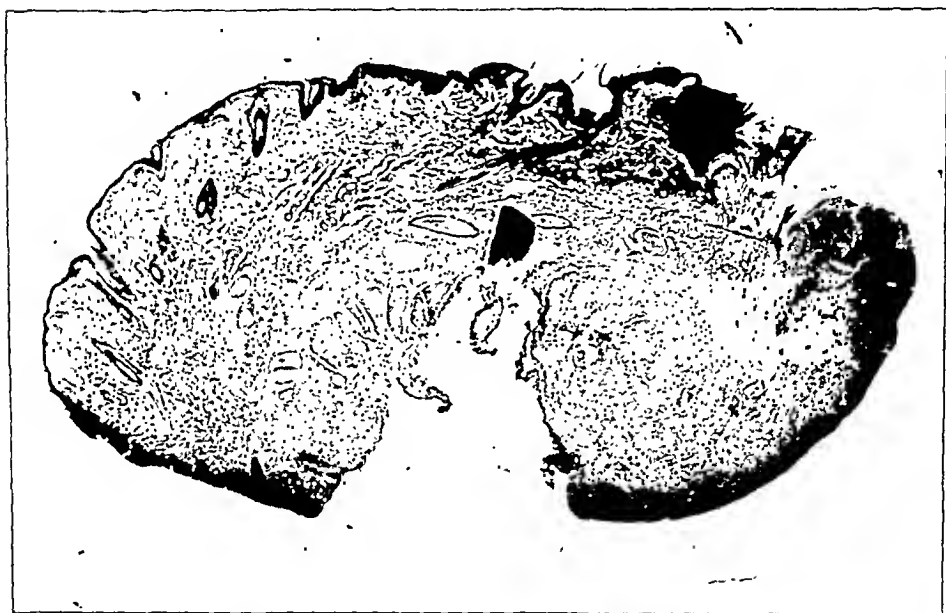

Fig. 6.—Photomicrograph of a section taken through the center of a flap removed at the end of seven days. There are many small, medium and large blood vessels in the subcutaneous tissue and in the deeper portion of the cutis vera. There is also early granulation tissue in the cutis vera containing many capillaries. A comparison of this section with that in figure 2 is interesting as it shows the marked increase of blood vessels both in size and number which have developed in seven days.

venules; these two networks are often termed the subpapillary venous plexus. The blood flows deeper by numerous tributaries to a third and fourth venous network, the former lying immediately deep to the subpapillary arterial plexus, the latter at the level of the cutaneous plexus of arteries, where cutis and subcutis join.

The general arrangement of the vessels is illustrated in the diagram (fig. 9), modified from that originally published by Spalteholz.

Thomas Lewis,[8] in his monograph on the blood vessels of the human skin, utilized a somewhat less involved terminology in distinguishing the various vessels, classifying them as strong arterioles, minute vessels and deep veins.

The classification used by Lewis is much simpler than that prepared by Spalteholz. If detail is desired in descriptions the classification of Spalteholz is to be preferred, but for ordinary use that of Lewis is sufficient.

The results of the experimental work have been so significant, that although we have not had the opportunity of making injections into
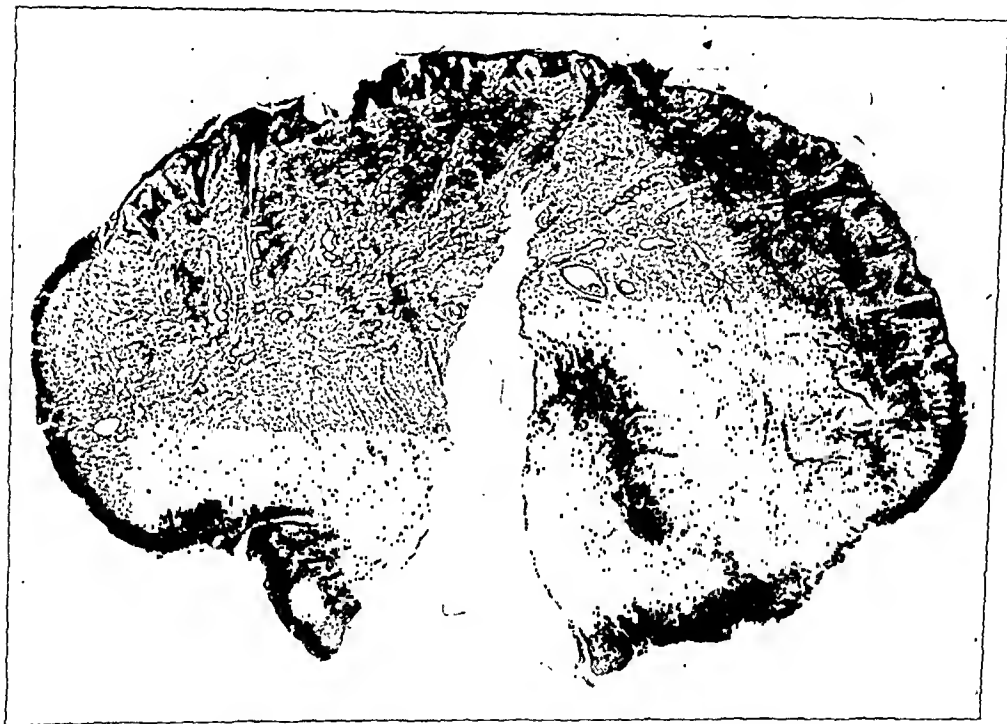

Fig. 7.—Photomicrograph of a section taken through the center of a flap removed at the end of eleven days. There are many small, medium and large blood vessels in the subcutaneous tissue and in the cutis vera. There is also well developed granulation tissue in the cutis vera. There is not much difference in the development of the blood vessels shown in this section and that shown in the seven day specimen in figure 6.

flaps on human beings, we feel justified in surmising from clinical observations along the same line that much the same process takes place as in the animal experiments, and that in a tubed flap the normal vessels of the human skin also increase in size and number and that the

8. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

main vascular channels are reoriented to correspond to the long axis
of the flap.

The information obtained from the animal experiments seemed
worthy of a careful clinical tryout. This was checked at first on
patients as follows. Tubed flaps which had been prepared for trans-
plantation to definite defects were used. We started with the division
of the pedicle on the fourteenth day and gradually reduced the time
until now in suitable cases we sometimes divide the pedicle on the tenth
day. However, we usually prefer to divide the selected pedicle
piecemeal, that is, a third or half way through on the tenth and the

Fig. 8.—Typical roentgenogram of a flap into which an opaque mixture was
injected and the flap removed at the end of fourteen days. There is little change
to be noted in the vessels on comparison of the fourteen and the seven day speci-
mens, either in number, character or size.

remainder on the eleventh or twelfth days, depending on whether the
separation is done in halves or thirds, and have adopted this as a
routine procedure in dealing with ordinary tubed flaps. Frequently
there is definite arterial bleeding from the end of the tube when the
pedicle is divided. This usually comes from near the central portion
of the flap, but sometimes is well to one side or the other.

From the experimental data we might be justified in starting this
division as early as the seventh or eighth day, but as yet we have not

chanced the loss of a portion of the flap by trying this out clinically and think it safer not to begin the division of the first pedicle until the tenth day (fig. 10).

If there is doubt in the mind of the operator as to the vitality of the tube in any particular case, it is, of course, advisable to delay the division for full two weeks, or as much longer as conditions require. From the standpoint of the comfort of the patient, there is usually no particular hurry in dividing the first pedicle. On the other hand, when to divide the base pedicle, when the flap comes from a distant part, say from the arm to the face, is a much more important matter to the patient, on account of the enforced irksomeness of the position. We
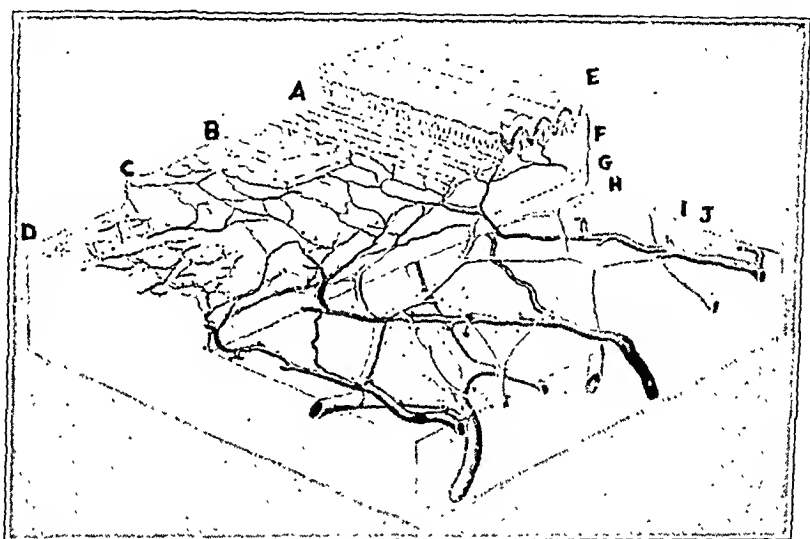

Fig. 9.—Diagram showing the arrangement of the human cutaneous blood vessels, Spalteholz' classification being used (Lewis). *A* and *B* indicate the subpapillary venous plexus (*A*, the first venous plexus and terminal arterioles and *B*, the second venous plexus); *C*, the subpapillary arteriolar plexus; *D*, the third venous plexus; *E*, the epidermis; *F*, the cutis; *G*, the arched arterioles; *H*, the fourth venous plexus; *I*, the sweat gland layer; *J*, the cutaneous arterial plexus.

have found that when the tube has been opened out for one-third its length or more and has been sutured in close contact with its new bed, that, all other conditions being favorable, we can begin to divide the pedicle as early as the eighth or ninth day and have the arm down on the tenth or eleventh day rather than wait two weeks as we had previously done. In these cases there is often profuse bleeding from both ends of the divided pedicle showing a good circulation originating in this period of time from the new base, as well as from the original source of blood supply.

Fig. 10.—The early division of pedicles and transference of a tubed flap from the arm to cheek. *A*, a tubed flap 13 cm. long formed on the inner side of the arm. This flap was planned in width, length and position to fill a defect to be made by the excision of a contracted scar of the cheek and lip. Note the complete formation of the tube, the type of pedicles and that the skin has been sutured beneath the tube. The lower pedicle was divided in stages beginning on the tenth day, and the division was completed on the eleventh day at which time the flap was opened for about half its length and was transferred and sutured, after raising the arm, into the defect on the cheek made by the excision of the contracted scar tissue and for which it had been prepared. *B* and *C*, the base pedicle on the arm was gradually divided beginning on the ninth day. Note the partial division in *B*. The division was completed on the tenth day. There was free bleeding from the stump attached to the cheek. This stump was opened and utilized. No portion of the flap was lost by the early division of either pedicle. *D*, the final result of the transfer of the tubed flap. Note the smooth normal looking skin which fits into its new environment quite naturally.

SUMMARY

The clinical application of the information obtained in this experimental study has been successfully tried out on tubed flaps during the last three years. It has also been of value in determining the time of division of the pedicles in those long pedicled flaps which are raised and without being tubed are immediately sutured back into the bed from which they came until ready for transfer.

The longer the tubed flap is allowed to remain intact, within certain limits, the more stable the blood supply becomes, but from our observations, both clinical and experimental, we are convinced that the establishment of circulation in tubed skin flaps occurs considerably earlier than was previously thought possible and consequently that it is safe to divide the pedicles sooner.

A PATH OF INFECTION IN PERINEPHRITIS

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Last year, before the Chicago Urological Society, Dr. Burstein and I reviewed a series of fifty-five cases of perinephritic abscess.[1] Thirty-two were metastatic in origin. The metastatic abscesses are of particular interest because they are usually diagnosed only when the condition has become well developed. They are, in the vast majority of cases, primarily cortical abscesses of the kidney,[2] thus accounting for the difficulty in their diagnosis. The abscess at first does not communicate with the renal pelvis, so that the urinary and pyelographic findings are negative until some weeks later, when the abscess has extended and communicates with the pelvis. The outer capsule undergoes inflammatory reaction and encapsulates the abscess, and thus here also evidence does not usually present itself until the abscess has spread into the perinephric tissue, when it is possible to make the diagnosis by the presence of a tumor, the finding of pus by aspiration or roentgenologic evidence.

The various modes of invasion in perinephritis are pictured in the accompanying diagram (fig. 1). One of the paths of extension of infection—that along the periureteral sheath, of which very little mention has been made in the literature—is here shown.

Since that report, I have operated in twelve cases of perinephritic abscess, one of which was bilateral. Two of these cases are of particular interest in that they indicate the path of infection as the sheath of the ureter. Other postoperative and postmortem observations are also of interest, for they show quite definitely the ureteral sheath as the pathway of infection from the pelvis upward and from the kidney down. These various observations prompted the experimental roentgenologic observations on postmortem specimens of kidneys, ureters and bladder, which will be reported. The various clinical observations will be briefly mentioned first.

REPORT OF CASES

CASE 1.—In a woman, five days after a normal labor, a chill developed, followed by a fever which persisted for weeks and which was septic. There were no pelvic or urologic findings. After six weeks some tenderness and rigidity in the right

loin prompted incision of this region. A large perinephritic abscess, which had extended in sacculations from the pelvis up to the kidney, was drained. Six weeks later, a left perinephritic abscess was drained. This abscess also extended along the posterior part of the peritoneum from the base of the bladder up to the kidney.

Case 2.—In a man aged 55, who gave a history and rectal findings of a chronic prostatovesiculitis, a septic temperature with some tenderness in the right lumbar region developed. Cystoscopic, urinary and roentgen findings were negative. A diagnosis of perinephritic abscess was made two weeks later by puncture and aspiration. At operation a large abscess, extending up to the kidney but lying in the dead space below it, was drained. Exposure of the ureter showed marked thickening and irregularity throughout its entire course from the bladder to the kidney.
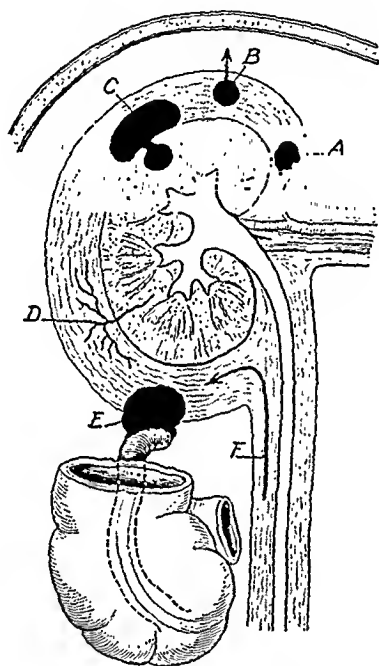

Fig. 1.—Diagram to show sources of perinephritic abscess. *A*, hematogenous form, face of infection elsewhere in body; *B*, extension of perinephritic abscess to subphrenic space; *C*, extension of infection from cortical abscess of kidney to fat around it; *D*, same as *C*, but by way of lymphatics; *E*, retrocecal appendiceal abscess extending to perinephric fat, and *F*, extension of infection from prostate, etc., along periureteral sheath. (*From Eisendrath and Rolnick:* Urology, Philadelphia, J. B. Lippincott Company, 1930, p. 690.)

In the first case, the abscess may have developed and extended upward by continuity along the posterior peritoneum from the base of the bladder to the kidney. It may also have extended along the sheath of the ureter.

In the second case, the evidence at hand, the previous prostatovesiculitis, with negative urinary findings, and the irregularity, thickening and beading of the ureter indicate extension along the sheath of the ureter. The abscess did not involve the perinephric tissue, for it

had most likely broken through the ureteral sheath at one or more points before extending to the kidney.

CASE 3.—Ten days following a low ureterotomy for stone, the patient required exposure of the kidney of that side because of pain, tenderness and rigidity over the lumbar region, together with chills and fever. An abscess was found which was entirely subcapsular and had no renal involvement.

Here also the extension of the infection, undoubtedly from the site of the ureterotomy wound, was either along the lymphatics of the wall of the ureter or more likely along the sheath of the ureter.

CASE 4.—Two days following a difficult nephrectomy in a case in which a small portion of the pelvis was left because it was bound down toward the median line very close to the vena cava, funiculitis of the spermatic cord of that side with some tenderness developed. This gradually subsided and cleared up completely when the patient left the hospital eighteen days following the operation.

CASE 5.—A nephropexy for kink of the ureter, in which the ureter was freed from adhesions, was followed within thirty-six hours by a rather marked crepitus of air emphysema in the spermatic cord of the same side high up in the scrotum. There was no scrotal emphysema. The patient made an uneventful convalescence, the emphysema clearing up within six days.

Cases 4 and 5 indicate rather clearly the path of the funiculitis and the air emphysema of the spermatic cord as the sheath of the ureter and by extension at the junction of the ureteral sheath with that of the seminal vesicle along the sheath of the vas to the external inguinal ring. A few years ago, I demonstrated the possibility of infection along the sheath of the vas,[3] and also presented clinical evidence of the same. Abscess and funiculitis usually present themselves in the groin at Bogros's space,[4] a loose band of connective tissue separating the pelvic from the scrotal vas.

CASE 6.—At operation for a transcapsular rupture of the kidney, a fairly marked hematoma was present; blood had also extravasated along the posterior peritoneum downward for some distance along the sheath of the ureter.

CASE 7.—Autopsy in a man who had a marked pelvic infection disclosed a calculus in the cavity of a prostatectomy wound of a year before. This had eroded through the prostatic capsule. The inflammatory involvement extended downward along the sheath of the vas up to the scrotal portion and also upward along the sheath of the ureter and posterior peritoneum up to the perirenal tissues.

These various observations of extension of infection from the pelvis upward and from the kidney downward, with no associated urinary findings, as shown in the first five cases, indicate the path of infection as

3. Rolnick, H. C.: Infections Along the Sheath of the Vas Deferens, J. Urol. **14**:371 (Oct.) 1925.

4. Belfield, W. T., and Rolnick, H. C.: Roentgenography and Therapy with Iodized Oils, J. A. M. A. **86**:1831 (June 12) 1926.

along the outer wall of the ureter or its sheath. The rapid extension downward of pus and air to the spermatic cord and of blood along the sheath of the ureter is strong evidence of extension of the process along the sheath of the ureter and by continuity along the sheath of the vas.

Considerable experimental work has been done on ascending infection of the kidney. Eisendrath and Schultz [5] showed that infection may extend upward along the anastomotic chain of lymphatics in the wall of

Fig. 2.—Postmortem specimen of bladder, ureter and kidney; the peritoneum is still attached to the ureter. The periureteral sheath is shown with injection of contrast medium throughout most of its length.

the bladder and ureter, and that ascending infection can develop in this manner secondarily from infection of the prostate and seminal vesicle.

Belfield,[6] in his classic paper on "Pus Tubes in the Male," described the intimate relation of the ureter, vesicle and vas as the broad ligament

5. Eisendrath and Schultz: J. M. Research **35**:295 (Jan.) 1917.
6. Belfield, W. T.: Pus Tubes in the Male, J. A. M. A. **53**:2141 (Dec. 25) 1909.

in the male and showed the close proximity of the fascia and sheath of the seminal vesicle with that of the ureter.

Von Lichtenberg [7] discussed pathologic involvement of the upper urinary tract secondary to adnexal disease in the male and showed varying degrees of hydronephrosis and renal infection resulting therefrom, some cases even requiring nephrectomy. These all resulted from compression of the lower part of the ureter by the seminal vesicle and stric-

Fig. 3.—Postmortem specimen of bladder, ureter and kidneys; contrast fluid is shown injected into both ureteral sheaths extending from the base of the bladder up almost to the kidney.

ture of the ureter, owing to extension of infection to the ureter from the prostate and seminal vesicles.

Considerable emphasis has been given of late to the importance of adnexal disease in the male in pathologic involvement of the upper urinary tract. Von Lichtenberg [7] spoke of the junction of the urinary and genital tracts in the male at the point where the vas crosses the

7. von Lichtenberg: J. Urol. **24:**1 (July) 1930.

ureter and the seminal vesicle comes in contact with the ureter as a bad corner. At this point, there is a common nerve, blood and lymph supply. The ureteral sheath communicates here with that of the seminal vesicle and also with the loose fascia at the base of the bladder in both males and females.

The sheath of the ureter covers the ureter along its entire course, extending upward from the base of the bladder, enveloping the renal

Fig. 4.—Various specimens showing the injection of the periureteral sheaths with contrast fluid at various points along their course.

pelvis and infiltrating and covering the fatty and true renal capsule. Within this sheath the ureter has considerable of its blood, lymph and nerve supply. In performing a ureterotomy for stone, it is best to leave the ureter attached to the peritoneum. Traction on the ureter and separation from the peritoneum may result in separating it from its sheath. Slough of the ureter and persistent fistulas may result from depriving it of its blood, lymph and nerve supply. It is, therefore, evident that the ureteral sheath is an important structure, and that it also permits possible extension of infection.

The periureteral sheath is also considered in Eisendrath and Rolnick's [8] "Urology" as a path of extension of infection to the perirenal tissue from the parametria, prostate, seminal vesicles and bladder.

EXPERIMENTAL DATA

The experiments for the purpose of determining the accuracy of the various clinical observations were made as follows:

Fig. 5.—Specimen showing the injection of the periureteral sheath of each side with contrast fluid practically its entire length.

Fresh postmortem specimens of both kidneys, ureters and bladder were employed. The specimens were from both males and females, children and adults; in all, thirty were obtained over a period of a few months. In the male the adnexae were also attached.

A contrast fluid of from 25 to 30 per cent sodium bromide solution was injected into the ureteral sheath, and the specimen was then roentgenographed. Injections were begun either in the fascia at the base of the bladder near the ureter or within

8. Eisendrath, D. N., and Rolnick, H. C.: Urology, Philadelphia, J. B. Lippincott Company, 1930, p. 689.

the sheath of the seminal vesicle. In others, injection was made directly into the ureteral sheath, beginning at the juxta vesicular portion of the ureter and extending upward. In a few specimens the injections within the sheath were begun at the renal pelvis and carried downward. In practically all instances, the contrast fluid could be forced very readily upward or downward along the sheath of the ureter. In the female, infiltration of the loose tissues at the base of the bladder permitted the forcing up and milking upward of the contrast medium in the ureteral sheath. The accompanying illustrations (figs. 2, 3, 4, 5 and 6) show the ureteral sheath into which contrast fluid was injected in the various ways mentioned.

Fig. 6.—In each of these specimens, pyelograms and ureterograms have been made of one side to show the contrast with the other side in which injection into the ureteral sheath has been made. On the left hand side injection has been made into the ureteral sheath, from the base of the bladder upward. Air has been injected into the lumen of the ureter. On the right hand side, a ureteral catheter has been inserted into the lumen of the ureter, and injection made into the ureteral sheath from the bladder upward.

COMMENT

This, I believe, is the first time that the possibility of extension of infection along the sheath of the ureter has been demonstrated roentgenographically. These clinical and experimental observations should be of particular interest to gynecologists as well as to urologists. There are many clinical observations by both gynecologists and urologists of adnexal and pelvic infection causing infection of the upper urinary tract.

The demonstration of extension of infection along the sheath of the ureter is of decided clinical importance.

Bands and adhesions about the ureter and renal pelvis, periureteritis, peripyelitis and perinephritis, acute and chronic and of varying degrees of severity, including perinephritic abscess, may result from extension of infection along the sheath of the ureter secondary to pelvic infection in both male and female.

Dr. Jaffé, pathologist at Cook County Hospital, and his associates procured the specimens used in these experiments.

Dr. Kaplan, radiologist at Mount Sinai Hospital, did the roentgenographic work on the specimens.

RESECTION OF SENSORY NERVES OF PERINEUM IN CERTAIN IRRITATIVE CONDITIONS OF THE EXTERNAL GENITALIA

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The purpose of this paper is to form some estimate of the efficacy of neurectomy of sensory nerves in the treatment of certain irritative lesions of the female external genitalia. The intolerable itching which may be associated with such conditions as kraurosis, leukoplakic vulvitis and pruritus of the vulva with or without lichenification is often particularly resistant to local medication, whether this consists in the application of drugs or in exposure of the region to roentgen or actinic rays. This distressing symptom not only leads to excoriation of the parts, but also reduces the physical and moral stamina of the patient by depriving her of sleep. Two surgical procedures are available for the treatment of these conditions: vulvectomy and section of the sensory nerves to the parts. The choice of operation may be simplified by the occasional appearance of malignant lesions in the course of one of these diseases, a matter that has been recently dealt with by one of us;[1] in such cases either simple or radical vulvectomy, according to the degree of malignancy, is obviously the correct treatment. In cases in which there is not any suspicion of malignant degeneration, section of the sensory nerves of the area avoids the element of mutilation inseparable from vulvectomy. At first sight it would appear that neurectomy is merely symptomatic treatment; however, we have evidence that this operation may have a healing effect on the cutaneous lesions. This evidence, with a description of the histologic appearance of the skin before and after operation, will be presented in a subsequent paper.

THE NERVES OF THE EXTERNAL GENITALIA

The pudic nerve (fig. 1) is derived chiefly from the third and fourth sacral segments of the spinal cord, and also receives a small contribution

1. Counseller, V. S.: Leukoplakic Vulvitis or Kraurosis Vulvae; Its Relation to Carcinoma and Its Surgical Treatment, Minnesota Med. **14**:312 (April) 1931.

from the second sacral segment. It enters the ischiorectal fossa around the lower border of the small sacrosciatic ligament, and runs on the inner aspect of the obturator internus muscle in a fascial tunnel known as Alcock's canal. At first it has the pudic artery and veins on its outer side, but soon takes up a position superficial to these vessels. Soon after its appearance in the fossa it gives off its inferior hemorrhoidal branches, which cross the space to supply the posterior part of the

Fig. 1.—The anatomy of the pudic nerve (Spalteholz).

external anal sphincter and the skin overlying this; not uncommonly, however, these branches arise directly from the sacral plexus and enter the fossa separately. The trunk itself courses forward and becomes more superficial; it ends by dividing into the perineal nerve and the dorsal nerve of the clitoris. Sometimes the trunk divides into these in the posterior part of Alcock's canal; sometimes its final division is delayed until it reaches the superficial transverse muscle; usually the separation into its terminal branches takes place about the middle of

Alcock's canal. Wherever they are formed, the perineal nerve lies superficial to the pudic vessels, and the dorsal nerve of the clitoris deep to them.

The perineal nerve almost at once divides into two branches: superficial and deep. The superficial perineal nerve is purely sensory, and passes forward to divide into the external and internal labial nerves, which may be traced at least as far as the middle of the labia majora; the external nerve usually goes superficial to the transversus perinei muscle, the internal nerve through or deep to that muscle. The external labial nerve anastomoses with the pudendal branch of the small sciatic nerve. The first offshoot of the deep perineal nerve is a branch for the anterior part of the sphincter ani externus. When the pudic nerve divides about the middle of Alcock's canal, this anal branch passes transversely to its destination; on the other hand, when the final division of the pudic nerve is delayed until it reaches the posterior border of the superficial transverse muscle, the anal branch curves backward and somewhat inward to reach the sphincter. The uncertainty of the course pursued by the anal nerve makes it necessary for the surgeon to identify and avoid it during resection of the sensory nerves of the area. The deep perineal nerve then leaves the fossa by passing deep to the superficial transverse muscle and between the two layers of the triangular ligament; it is expended chiefly in the supply of the muscles in the anterior part of the perineum: the superficial transverse muscle, the posterior part of the constrictor urethrae,[2] the ischiocavernosus and the sphincter vaginae; it also sends branches to the bulb of the vestibule.

The dorsal nerve of the clitoris passes between the two layers of the triangular ligament, in company with the pudic artery; in this part of its course it gives motor fibers to the anterior part of the constrictor urethrae. Close to the symphysis it pierces the triangular ligament and ends in the supply of the clitoris.

The small sciatic nerve, which is derived from the first, second and third sacral nerves, also contributes to the sensory innervation of the external genitalia. One of its descending branches, the pudendal branch, runs mesially and forward, and courses toward the vulva about 2 cm. lateral to the ramus of the ischium. Finally, it pierces the deep fascia, and after anastomosing with the external labial nerve, it is distributed to the posterior half of the labium majus, and to the adjacent part of the skin of the perineum.

The anterior third of the labium majus derives its sensory supply from the terminal branches of the ilio-inguinal nerve and the genital

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2. Including that part of this muscle sometimes separately described as the transversus perinei profundus.

branch of the genitocrural nerve. The ilio-inguinal nerve is derived from the first, and the genitocrural from the first and second lumbar segments of the spinal cord.

The cutaneous areas subserved by each of the main sensory nerves are shown in figure 2, which has been modified from Tavel.[3] On account of the rich anastomosis between their terminal twigs, the area supplied by each nerve is not sharply demarcated, and as a corollary the division of any one of them does not lead to complete paralysis of sensation in the territory attributed to it. This is especially the case with the labial nerves, the fine terminal branches of which often appear to overlap the field of the ilio-inguinal and genitocrural nerves. However, sensation
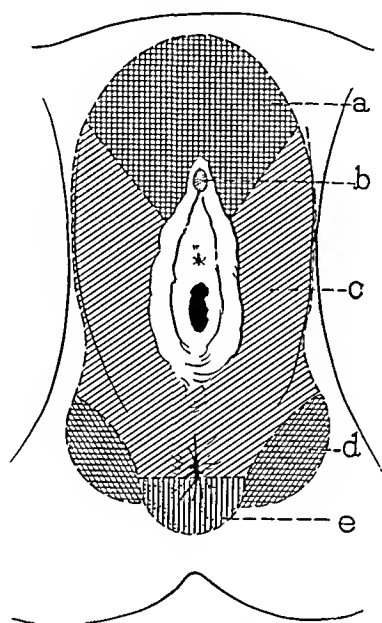

Fig. 2.—The cutaneous distribution of the nerves of the perineum in the female (modified from Tavel): *a*, ilio-inguinal and genitocrural nerves; *b*, dorsal nerve of clitoris; *c*, superficial perineal nerve; *d*, pudendal branch of small sciatic nerve, and *e*, inferior hemorrhoidal nerve.

in the posterior two thirds of the labia majora may be greatly blunted by division of the superficial perineal nerves and the pudendal branches of the small sciatic nerves; the clitoris may be added to this area by division of its dorsal nerves.

From an analysis of the sensory innervation of the perineum, it will be apparent that in order to allay irritation about its hinder part, the surgeon should aim at dividing the superficial branches of the perineal

3. Tavel, E.: La résection du nerf honteux interne dans le vaginisme et le prurit de la vulve, Rev. de chir. **25**:145, 1902.

nerves, the pudendal branches of the small sciatic nerves and, if necessary, the dorsal nerves of the clitoris. The muscular branches of the deep perineal nerves to the anterior part of the sphincter ani must be carefully preserved; the nerves to the posterior part of the sphincter ani are not likely to be displayed during the operation.

TECHNIC OF OPERATION

For seventy years sporadic reports of operations on the pudic nerves have appeared in surgical and gynecologic literature. Most of these reports attribute the first operation to Sir James Y. Simpson [1] of Edinburgh, but give a reference to one of his papers which does not allude to neurectomy. The correct reference [4] contains a description of the procedure, under the heading "Hyperaesthesia and Neuralgia of the Vulva," and gives priority in its use to Dr. Burns of Glasgow. This description is quoted to show the first step in the evolution of the operation. It may be added that the temporary nature of the results obtained by the original method were obviously due to regeneration of the nerves.

"There is one other morbid condition of the female genital organs, regarding which you must allow me to say a word or two during the few minutes we have still at our disposal. It is observed chiefly in married women who come to you complaining that contact with a certain point in the sides of the vaginal orifice, or vulva, causes them such acute suffering that they are totally unable to endure any attempt at marital intercourse. This pain seems to be due to a state of hyperaesthesia of the pudic nerve, and was first described by Dr. Burns, of Glasgow, who, in his Principles of Midwifery, after describing the anatomical distribution and relations of the nerve, goes on to say that it 'is often preternaturally sensible, so as to cause great pain in coitu, as well as at other times. It may be exposed, by cutting through the skin and fascia, at the side of the labium and perineum; beginning on a line with the front of the vaginal orifice, and carrying the incision back for two inches. The nerve being blended with cellular substance is not easily seen in such an operation; but it may be divided by turning the blade of the knife, and cutting through the vagina to its inner coat, but not injuring that. It may be more easily divided by cutting from the vagina. Slitting, merely, the orifice of the vagina will not do; we must carry the incision fully half an inch up from the orifice, and also divide the mucous membrane freely in a lateral direction.' I formerly knew one or two patients who had consulted Dr. Burns in regard to this affection, and in whom the pudic nerve had been divided in the manner he describes, either by himself or by his son; yet in these patients the painful sensation returned, though sometimes not in the same place, but in the track of some other nerve. I believe, with Dr. Burns, that the best palliative treatment for such cases is division of the affected nerve; but, instead of laying it bare, I have usually cut it through subcutaneously, by means of an ordinary tenotomy knife. It is a surgical measure far more simple in its character. Occasionally there is greater supersensitiveness and neuralgia of the vulva and vaginal orifice, without there existing any local lesion whatever capable of accounting for it. The pain is not then usually limited to any one single point. Such cases require the usual constitutional treatment of neuralgia, as iron, manganese, arsenic, etc., sometimes in long-continued

4. Simpson, J. Y.: Clinical Lectures on the *Diseases of Women*: Lecture 10. On Caruncles of the Urethra—Neuromata of the Vulva—Hyperaesthesia and Neuralgia of the Vulva, M. Times & Gaz. **39**:333 (April 2) 1859.

courses. You have to use general anti-neuralgia tonic medicines and measures; and locally all forms of sedatives and anodyne applications."

Alternative methods for resecting the nerves of the perineum have been described by Rochet [5] and Tavel, and recently by Wertheimer and Michon.[6] It is possible to approach the resection by either of two plans: by finding the trunk of the pudic nerve, and then tracing it peripherally to the desired branches, or by finding certain peripheral branches and tracing them proximally to the terminal branches of the trunk. In our experience the second method has proved satisfactory (figs. 3 and 4).

The patient is placed in an exaggerated lithotomy position, and the parts are prepared. The steps of the operation are the same on both sides. The length of the incision varies from 7.5 to 10 cm., depending on the obesity of the subject. It is placed parallel to and about 3 cm. from the rami of the ischium and pubis, about
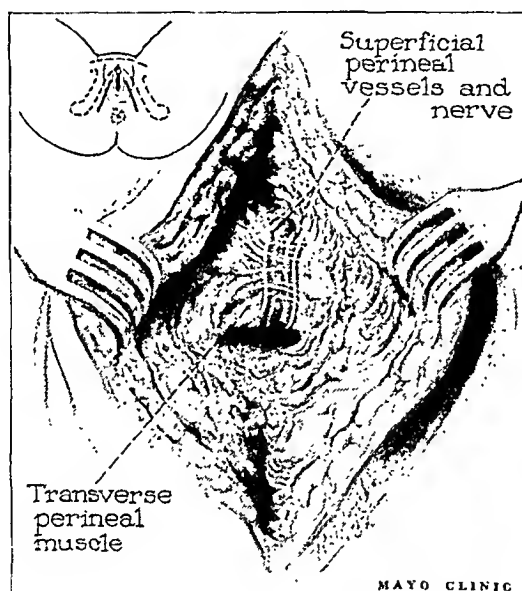

Fig. 3.—Division of nerves of vulva, first stage.   Inset, the incisions.

five sixths of it being anterior to the anus. An incision so placed rarely gives rise to subsequent discomfort in walking or sitting. The incision is deepened by blunt dissection until the posterior border of the superficial transverse muscle is reached. The superficial perineal packet of vessels and nerves is then isolated as it turns forward around the muscle. It is not unusual for this packet to contain only the inner of the two labial nerves; the outer labial nerve should then be sought as it turns around the border of the muscle. We have not found it of any advantage to attempt to preserve the small arteries and veins in the packet; it is divided between two clamps. The outer nerves in the grasp of the distal clamp are then traced distally, in an attempt to find their anastomosis with the pudendal branch

5. Rochet, V.:   Traitement chirurgical des prurits périnéaux, anaux et vulvaires, Lyon méd. **100**:570, 1903.

6. Wertheimer, P., and Michon, L.:   La névrotomie du nerf honteux interne: indications, technique, résultats. J. de chir. **31**:497 (April) 1928.

of the small sciatic nerve; if the latter is reached it is divided and its distal portion is twisted out. If it is not reached, the labial nerves and vessels are ligated as far forward as possible, or twisted out, and the tissues thus isolated are removed. The nerves in the grasp of the proximal clamp are then traced proximally until the perineal branch of the pudic nerve is reached. The twigs of this nerve that run to the anal region are carefully safeguarded; if it is necessary to denervate the skin of this area, each terminal twig must be tweaked; only the twigs that depress the skin when tweaked are to be resected. The branches between the perineal nerve and the proximal clamp are removed, after ligation of any vessels. In this way a segment of the labial nerves from 5 to 8 cm. long may be resected, and a segment from 2 to 3 cm. long of the sensory branches of the perineal nerve to the skin around the anus.
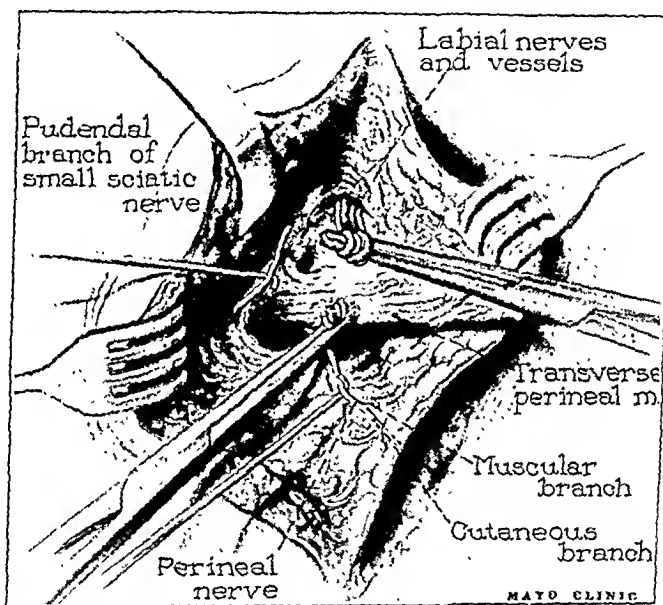

Fig. 4.—Division of nerves of vulva, second stage.

If the dorsal nerve of the clitoris is to be resected, it may be found deep to the pudic artery, by following the perineal nerve (or bundle of nerves) toward the pudic trunk on the surface of the obturator internus muscle. Alternatively, if the division of the pudic nerve has taken place in the posterior part of its course, the dorsal nerve of the clitoris may be sought directly in Alcock's canal.

If it has been impracticable to isolate the pudendal branch of the small sciatic nerve in front, an attempt may be made to find the branch as it approaches the perineum. It runs parallel to and about 2 cm. to the outer side of the ramus of the ischium, and may be sought in this situation after retraction of the outer lip of the wound.

The deep layers of the wound are then approximated by a few points of catgut, and the incision in the skin is closed. We have not found it necessary to employ drainage. A similar procedure is then carried out on the opposite side. The postoperative treatment does not differ from that of any other operation on the perineum.

PREVIOUSLY RECORDED OPERATIONS

Two cases have been recorded by Rochet: [5]

A woman, aged 48, had pruritus for more than ten years; even the vagina and the urethra itched. Apparently the trunk of the pudic nerve was divided on both sides; the pudic vessels were preserved. The itching was relieved for at least three years.

A man, aged 50, had pruritus of the anus and scrotum for two years. The superficial branches of the perineal nerve, its branches to the skin around the anterior part of the anus and the pudendal branch of the small sciatic nerve were divided on both sides. The patient was completely relieved, and the cure persisted for at least eight months.

One case has been recorded by Murard: [7]

A woman, aged 54, underwent subtotal hysterectomy in 1922, under spinal anesthesia. A day or two after the operation she began to have symptoms of two distinct types: a feeling of weight in the perineum, with a sensation of fulness in the bladder leading to frequency, and pruritus of the vulva. Seven years after the original operation, the pudic nerves were divided on both sides. Five weeks later the pruritus had disappeared, and the parts appeared healthy. The presence of the perineal scars gave rise to a little inconvenience in walking Murard was of the opinion that an injury to the roots of the cauda equina during the administration of the spinal anesthetic was the exciting factor in the case, but in the discussion which followed its presentation, Basset stated that an analysis of a large series of cases in which spinal anesthesia was used did not lend support to this view.

One case has been recorded by Mauclaire: [8]

A woman, aged 34, two months after a pelvic operation, began to suffer from intense vulvovaginal pruritus, much pelvic pain and some vaginismus. At a second laparotomy, adhesions were separated and the remaining ovary was partially resected. The pruritus became worse. Eight months after the original operation, the right dorsal nerve of the clitoris and the left perineal nerve were resected. The patient was relieved of her symptoms, except that some vaginismus persisted.

One case has been recorded by Albertin: [9]

A woman had suffered for eight years from pain in the bladder and vulvovaginal pruritus. On the right side the resection was limited to the perineal nerve, and on the left side the pudic nerve and artery were resected. The pruritus was relieved for the forty-five days the patient remained under observation. It is noteworthy that, after the neurectomy, the passage of a catheter could still be felt.

One case has been recorded by Tavel: [3]

A woman, aged 48, had suffered for a number of years from pruritus of the vulva, and an extreme degree of vaginismus. On the right side the perineal nerve

7. Murard, Jean: Troubles vaso-moteurs et hyperesthésiques consécutifs à une rachianesthésie. Traitement par névrotomie des honteux internes, Bull. et mém. Soc. nat. d. chir. **55**:1153 (Nov. 6) 1929.

8. Mauclaire, P.: A propos du prurit vulvaire traité par le névrotomie bilatérale des nerfs honteux internes, Bull. et mém. Soc. nat. d. chir. **55**:1210 (Nov. 30) 1929.

9. Albertin: Résection des nerfs honteux internes, Lyon méd. **100**:572, 1903.

was avulsed, its anal branch being preserved; on the left side the perineal nerve was avulsed in its entirety. Three months later the patient was entirely relieved, but had a little trouble in retaining a liquid stool.

One case has been recorded by Bérard and Wertheimer: [10]

A woman, aged 52, had had intense pruritus of the vulva for fifteen months. This resisted local treatment and periarterial sympathectomy of both internal iliac arteries. The perineal branch of the pudic nerve was divided on both sides. The result was excellent; not only was there symptomatic relief, but the cutaneous lesions were much improved. Two years later the patient had a mild recurrence of itching, which yielded to rest in bed.

CASES OBSERVED AT THE MAYO CLINIC

CASE 1.—A woman, aged 45, came to the clinic on Oct. 31, 1930, complaining of itching of the vulva which had begun in 1928, after panhysterectomy. The patient had not obtained satisfactory relief from local applications. About the clitoris, and between the fourchet and the anus, were several rough and elevated whitish patches. The vulva was markedly atrophied. A diagnosis was made of kraurosis of the vulva and beginning leukokeratosis near the fourchet.

On November 13, a specimen of skin was removed immediately posterior to the fourchet. Thereafter both branches of the superficial perineal nerve were divided, on both sides, at the posterior border of the superficial transverse muscle; the pudendal branch of the small sciatic nerve was also divided on both sides. On December 1, the wounds had healed, after some drainage from the wound on the left. The patient expressed herself as completely relieved. Two days later a dermatologist assessed the decrease in leukokeratosis at 75 per cent. On Jan. 9, 1931, the patient's family physician wrote that the vascularity of the tissues was much increased, and that the itching had disappeared entirely. An area 1 cm. in diameter to the left of the clitoris was still white and caused discomfort at times. In December, 1931, the patient was well pleased with the result of the operation.

The tissue removed showed the histopathologic picture of leukoplakia.

CASE 2.—A woman, aged 49, came to the clinic on Nov. 28, 1930, complaining of intense itching of the vulva of four years' duration. This had resisted treatment by local measures. On the inner aspects of the labia majora the skin was thick and white, and showed numerous excoriations at their upper angle. The labia minora were absent. There was relatively little atrophy of the skin, the latter being for the most part thick, white and soggy. A diagnosis was made of pruritus of the vulva, which some authorities would possibly term kraurosis in the hypertrophic stage.

On December 4, the perineal branches of the pudic nerve were divided on both sides. The pudendal branch of the right small sciatic nerve alone was divided; that of the left nerve was not identified. A portion of skin was removed for examination. On December 19, itching was still felt at night. A small area of soggy skin was still present around the clitoris. On Feb. 16, 1931, some itching was still present on the right side. On Jan. 13, 1932, the patient reported that she had had little relief from the operation, and that the presence of the perineal scars somewhat interfered with walking.

Sections of the skin removed at the operation showed the histopathologic picture of kraurosis of the vulva in its hypertrophic stage.

10. Bérard, L., and Wertheimer, P.: Kraurosis vulvae. *Névrotomie des nerfs honteux internes*. Guérison, Lyon chir. **23:**524, 1926.

CASE 3.—A woman, aged 61, came to the clinic on Feb. 28, 1931, complaining of itching about the anus and vulva, of nine years' duration. This had been treated elsewhere by injections of alcohol about the anus and external genitalia, but without success. The vulva was edematous and swollen. The mucous membrane was blanched, and there was a small area of necrosis and sloughing on the inner aspect of one labium majus. The skin on the inner aspects of both thighs was mildly irritated. The perianal skin showed similar but less severe lesions. A diagnosis was made of kraurosis of the vulva and anus, and leukoplakic vulvitis with lichenification and abrasions.

On March 4, the perineal nerve on the right side was divided, including a branch to the skin around the anus, and a similar resection was performed on the left side. The pudendal branches of the small sciatic nerves were not divided. A small piece of skin was removed for examination. On March 25, the vulva was less gray and more pinkish. There was not any evidence of scratching or leukoplakia. On June 1, scratch marks and erythema were both absent. The vulva had the usual light pink tint seen in older life. The patient was completely relieved of the itching.

The skin from the vulva showed the microscopic features of both kraurosis and leukoplakia.

CASE 4.—A woman, aged 49, came to the clinic on June 29, 1931, complaining of intense itching about the vulva, of thirteen years' duration; at times this had been so intense that the parts had been scratched until they were raw. Local treatment had not been of any avail. She had had some trouble in controlling the rectal sphincter. A diagnosis was made of pruritus of the vulva, with slight kraurosis, and mild prolapse of the rectum.

On July 8, the neurovascular packet containing the right superficial perineal nerves and vessels was divided. On the left side the vessels were dissected from the nerves, and only the latter were resected. During the dissection the right pudic artery was wounded and had to be tied, and the trunk of the right pudic nerve was also divided. A small piece of skin was removed for histologic study.

On July 20, the patient was relieved of the itching. She still had some trouble in controlling the rectal sphincter. On August 25, she reported that she had complete relief from itching; the rectal trouble persisted. On Feb. 5, 1932, she reported that the operation had been "a perfect success."

The skin from the vulva showed the histopathologic picture of neurodermatitis.

CASE 5.—A woman, aged 55, came to the clinic on July 9, 1931, complaining of itching of the vulva of thirteen years' duration. Local treatment had not resulted in improvement. Around the vulva and anus there were pigmentation, excoriation and definite atrophy involving the inner aspects of the thighs as well as the vulvar folds. Patches of superficial ulceration were present in these areas. A diagnosis was made of kraurosis of the vulva.

On July 24, an ulcerated area near the clitoris was removed for histologic examination. Thereafter the superficial perineal branches of the pudic nerve and the pudendal branch of the small sciatic nerve were resected on both sides. On August 8, the patient was completely relieved of itching. On Jan. 16, 1932, she reported that her condition was greatly improved; a little itching about the urethra was still present, at night only.

The portion of skin removed showed the histopathologic picture of leukoplakia.

CASE 6.—A woman, aged 40, came to the clinic on Aug. 27, 1931, complaining of itching of the vulva of ten years' duration. The first lesions had appeared on the inner aspect of the right thigh. After various local measures had been tried,

a series of applications of radium was made (elsewhere) over the vulva. The labia majora were edematous and red. Their skin was atrophic and contained numerous telangiectatic vessels. Above the clitoris were several moderately deep crusted ulcerated lesions, involving both labia. A diagnosis was made of pruritus and actinodermatitis of the vulva.

On September 1, the superficial perineal nerves and the pudendal branch of the small sciatic nerve were divided on both sides. On September 15, the itching had disappeared. In spite of their unfavorable situation both wounds had healed by primary union. On Jan. 12, 1932, the patient reported that she was in excellent condition and had no itching, and that all the ulcerated areas had remained healed. A biopsy was not performed in this case.

CASE 7.—A woman, aged 55, came to the clinic on Aug. 11, 1931, complaining of itching of the vulva of four years' duration. A diagnosis was made of kraurosis, involving the labia minora and clitoris.

On August 19, a specimen was removed for histologic examination; the superficial perineal nerves and the pudendal branch of the small sciatic nerve were resected on both sides. On September 2, the only itching area remaining was a small patch near the clitoris, where skin had been removed. On September 17, the patient reported that there had been some discharge from both wounds. On November 2, a further report stated that the itching had almost completely disappeared. In January, 1931, the patient reported that she had periods of itching about three times in each twenty-four hours.

The skin removed at operation showed the histopathologic picture of kraurosis of the vulva.

FUNCTION AFTER OPERATION

The Depth of Sensory Paralysis.—It has been pointed out that the sensory supply of the female genitalia is not demarcated in strict zones, so that an accurate assessment of the sensory changes which result from neurectomy is difficult. We have found that the area of blunting of sensation corresponds fairly closely to the territory assigned in figure 2 to the perineal nerves, although an attempt has not been made to separate their territory from that of the pudendal branches of the small sciatic nerves. In one of our successful cases tactile sensibility was not absent, although it was somewhat depressed, the principal change observed being analgesia, graded —2 to —3 on a basis of 4. Although single, this is an interesting physiologic observation, for elsewhere in the body the division of a sensory nerve usually produces more extensive anesthesia than analgesia. As a corollary it is of interest that the irritation which is called itching was suppressed in an analgesic area, although touch could still be felt; the orthodox view appears to be that itching is felt by way of tactile fibers. We were unable to detect any such dissociation of anesthesia in our remaining cases.

The Control of the External Sphincter of the Anus.—The posterior fibers of the external anal sphincter receive their motor nerves through the inferior hemorrhoidal branches, the anterior fibers from the perineal branches. The preservation of the inferior hemorrhoidal nerves is scarcely a matter for concern, because they do not hamper the operator

and indeed may not appear in the field. More care is necessary to preserve the muscular branches to the anus that are derived from the perineal nerve; they were divided on one side in Tavel's case, without any gross loss of rectal control. Division of the trunks of the pudic nerves distal to their inferior hemorrhoidal branches would leave the motor nerves to the posterior half of the sphincter intact, and in these circumstances it is likely that the combined action of the smooth internal sphincter and the posterior half of the external sphincter would assure control, except of liquid stools and after the administration of purgatives.

The Control of the Constrictor Urethrae.—In women the striated muscle fibers surrounding the urethra lack the purposive arrangement
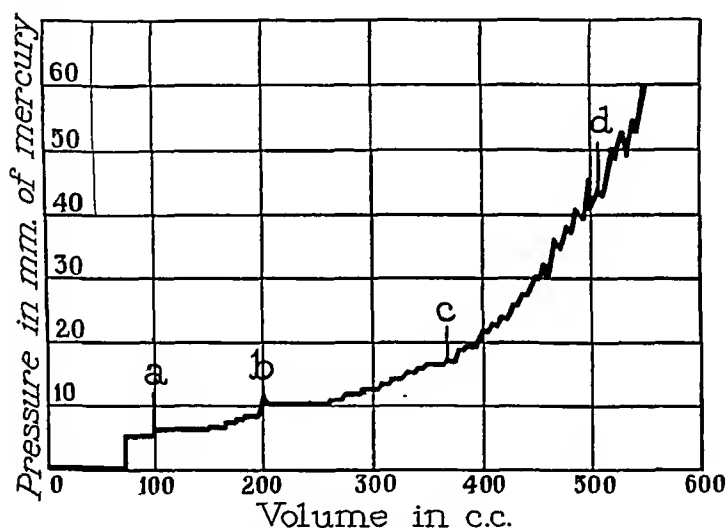

Fig. 5.—Normal cystometrogram, after division of the right pudic nerve and the left superficial perineal nerve: *a,* first appreciation of cold; *b,* first desire to void; *c,* first feeling of pain, and *d,* severe pain.

found in men. For the most part, they are set irregularly among the smooth muscle fibers that surround the wall of the tube. A part of this striated system is sometimes separately described as the transversus perinei profundus, and has assigned to it a function comparable to that of the external sphincter in men. This part of the sheet of striated muscle that closes the pelvic outlet in its anterior half can scarcely function as a true sphincter, because its fibers pass only behind the urethra, and form a sling for it rather than a circular controlling muscle.

The sheet of striated muscle fibers around the urethra receives motor nerves from the deep branch of the perineal nerve and from the dorsal nerve of the clitoris, the territory of the latter nerve being anterior to

that of the former; although its arrangement in the female is not mechanically adapted to function as a sphincter, the question of control of the bladder after operations on the pudic nerves is naturally of great importance. When the resection is limited to the purely sensory superficial perineal branches this question does not arise, but when it is desirable to divide the deep perineal branch and the dorsal nerve of the clitoris the surgeon must be able to assure his patient that the operation will not be followed by vesical incontinence. This sequel has not followed neurectomy, either in our hands or in those of others; evidently, in women, the smooth sphincter is sufficient to provide, not only for retention of the urine, but for its periodic evacuation. If any branches of the pudic nerves played an essential part in vesical control, incontinence of urine ought to have followed operation in our case 4, in Rochet's case 1, in Murard's case, in Mauclaire's case and in Albertin's

Neurectomy of Perineal Nerves

Observer	Patient Observed; Time	Result
Rochet	3 years	Completely relieved
Bérard and Wertheimer..	2 years	Slight temporary recurrence after two years
Learmonth	14 months	Almost completely relieved
Learmonth	13 months	Little, if any, relief
Rochet	8 months	Completely relieved
Learmonth	7 months	Completely relieved
Learmonth	6 months	Almost completely relieved
Learmonth	4 months	Completely relieved
Learmonth	4 months	Almost completely relieved
Learmonth	3 months	Completely relieved
Tavel	3 months	Completely relieved
Albertin	7 weeks	Completely relieved
Murard	5 weeks	Completely relieved
Mauclaire	Not stated	Relieved of pruritus; some vaginismus persisted

case. In our case 4, a normal cystometrogram was obtained after the operation (fig. 5).

CONCLUSIONS FROM RESULTS OF OPERATIONS

The results of the fourteen operations reviewed in this paper are best tabulated according to the period during which the patient remained under observation (table).

Experience has shown that the immediate effect of operation is to banish the pruritus. This desirable result has been absent in only one case (our case 2). We have not been able to explain this failure, as a result either of difficulty in performing the operation, or of any peculiarity of the vulvar lesion; it must be accepted as a failure. Granted that immediate relief is the rule, it is obvious that the permanence of relief depends on the possibility of regeneration in the severed nerves; therefore, only the first four cases in the table are of value in assessing the late results of operation. In case 1 the result might well be called permanent. In case 2 the possibility arises that the recurrence after the elapse of

two years was due to the restoration of additional sensibility to the skin, although the temporary nature of the recurrence is against this view. In case 3, the interval since operation is scarcely long enough to permit labeling the result permanent. In case 4 the result was a failure from the first. In the remaining ten cases, assessment of the immediate relief alone can be made; this was satisfactory in all.

It follows that every care must be taken at operation to resect or twist out sufficient lengths of the desired nerves to reduce the likelihood of restoration of their continuity. In their course the superficial perineal nerves undergo a sharp change in direction, and moreover their origin from the perineal nerve is on a substantially deeper plane than is their cutaneous distribution. It appears to us that the restoration of any considerable degree of innervation is unlikely in the territory of the labial nerves. It is otherwise for the nerves supplying the skin anterior to the anus. Their direction and plane correspond to those of the parent nerve, and it is not possible to resect more than a short segment of them; to guard against regeneration, the parent branches may be doubled back and tied in this position.

The operation appears to be well borne. Two patients in the complete series complained that the perineal scars interfered with walking; in one of these (our case 2) the operation had been totally ineffective, and in the other (Murard's case) the surgeon was unable to detect any alteration in the gait of the patient. We have indicated that a carefully performed operation does not prejudice the function either of the bladder or of the rectum.

To sum up, we feel that neurectomy may well be offered to patients suffering from irritative conditions of the vulva, except those of two types: When there is any suspicion of malignant change, vulvectomy is the only procedure to be considered, and when the patient is so fat that identification of the various nerves would be tedious and perhaps uncertain, vulvectomy provides the quickest solution of the problem.

SUMMARY

The anatomy of the sensory nerves of the perineum is described.

The operation of neurectomy of the sensory nerves of the perineum is described.

Fourteen cases are considered in which this operation has been performed for irritative lesions of the vulva.

The number of cases and the length of time they have been observed do not permit an opinion as to the permanence of the relief afforded by the operation. Nevertheless, it is recommended as the primary treatment in such cases, unless there is any suspicion of malignant change, or the patient is so obese that neurectomy would be difficult and uncertain.

ACUTE ABDOMINAL SYMPTOMS IN ARACHNIDISM

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Several cases of arachnidism, a clinical syndrome due to the bite of the "black widow" spider, the Latrodectus mactans, seen recently at the University of Virginia Hospital presented abdominal symptoms of great severity. If the true condition had not been recognized, exploration of the abdomen for an acute surgical abdominal emergency might have been readily undertaken. The ease with which this confusion might occur—witness the reports of several such patients subjected to operation elsewhere—and the apparent lack of consideration given the subject in the surgical literature suggested this résumé of arachnidism with particular reference to its abdominal manifestations.

The first case af arachnidism that came to my attention, case 1 of the series reported herewith, was not seen until the symptoms had commenced to subside, and the diagnosis was not made until several weeks after the patient had been discharged from the hospital. The diagnosis was made at that time through a conversation with a surgeon [1] in a neighboring city. He described the case of a man who had been sent to him a short time previously for operative treatment of a suspected perforation in a peptic ulcer. He felt that the symptoms and signs were not entirely typical and asked a medical consultant to see the case with him. The internist suspected arachnidism and elicited the fact that the patient had been bitten by a spider a few hours previously. Had this diagnosis not been made, the patient would have been subjected to an exploratory laparotomy for the suspected perforation of a peptic ulcer.

After hearing the symptoms and signs of this case described, I reviewed the history of case 1 and found them to be almost identical. With this background, it was not unduly difficult to make the correct diagnosis in the subsequent cases of the series reported herewith. In fact, case 2 created so much interest that the intern staff made the diagnoses in the later cases and admitted the last two patients, not to the surgical wards as candidates for operation, but to the medical wards for teaching purposes.

REPORT OF CASES

CASE 1.—C. L. S., a white man, aged 29, was admitted to a private room in the University of Virginia Hospital at 7 p. m. on Oct. 10, 1930. He complained of

1. Bigger, I. A.: Personal communication.

rather severe pain in the abdomen. He had awakened at 5 a. m. with a slight tingling pain in the left popliteal space. He had not noticed any swelling or redness at the site. The pain had gradually radiated up the left leg to the scrotum and the left groin. In a short time he had been seized with excruciatingly severe, cramplike pain throughout the abdomen and toward the region of the left kidney. He had consulted his family physician, who had suspected renal colic and had administered morphine by hypodermic injection. He had been slightly relieved, but the cramplike pains had persisted, with exacerbations at intervals of three or four minutes, throughout the day. Because of the persistence of the pain, the patient had consulted another physician, who sent him to the hospital and asked me to see him in consultation.

At that time a careful review of the history revealed nothing additional of positive value. There was no knowledge of any recent blow, injury or insect bite. There had been no urinary symptoms, no nausea or vomiting, and the bowels had moved normally that morning.

Examination revealed a well nourished young man in obvious pain, restless and somewhat anxious looking. His temperature was 99.6 F. by mouth; the pulse rate was 52 per minute, and his respiratory rate, 36 per minute. His respirations were rather shallow and somewhat labored. The blood pressure was elevated. There was no evidence of redness, swelling or heat and no pain or tenderness in the popliteal space, the left thigh, the groin or the scrotum. The abdomen was slightly tender throughout, and there was marked rigidity of the abdominal muscles, which felt boardlike. There was a little tenderness in the region of the left kidney. There seemed to be no abnormality of the muscle or tendon reflexes. Repeated urinalyses failed to demonstrate white or red blood cells, and there was no sugar or albumin in the urine. The leukocytes numbered 14,000 per cubic millimeter of blood.

No definite diagnosis was made. The perforation of a peptic ulcer was considered, but there was something indefinable about the consistency of the abdomen, which taken in conjunction with the absence of nausea and vomiting, the slow pulse rate, and the peculiar onset of the symptoms did not seem consistent with this diagnosis. Because of the pain in the left leg and the region of the left kidney, the tentative diagnosis of renal colic was made and continued careful observation advised.

The next morning the patient's pain had subsided to a considerable degree, and the tenderness and rigidity of his abdomen were scarcely perceptible. His temperature was normal, and the leukocytes numbered 12,500. Later that day he felt well enough to go home, and was allowed to do so.

For a few days he was followed by the medical consultant as an office patient, and repeated urinalyses still failed to reveal any abnormal findings. Five days later a small, slightly indurated area was palpable in the left popliteal space. It soon disappeared, however. The patient's history was filed under "no diagnosis." As previously mentioned, the diagnosis of arachnidism was not realized and made until several weeks later, after hearing the history of a case from a surgeon of another city.

CASE 2.—T. D., a white man, aged 21, was admitted to the surgical ward service of the University of Virginia Hospital on Sept. 20, 1931, at 3:30 p. m. He complained of severe pain in the abdomen. He had arisen that morning feeling perfectly well, had eaten fried ham, bread and coffee for breakfast at about 9 a. m., and then had gone to an outhouse toilet and had a normal bowel movement. While there he had not been conscious of anything like the bite or sting of an insect. Half an hour later he had started out of his house but had been seized

suddenly with such a severe pain in the lower part of his abdomen on the right side and extending to the right groin that he had gone back into the house to lie down. The pain had increased so much that he had called his family physician, who administered morphine hypodermically. The pain had persisted, and the physician had sent the patient to the hospital because he suspected some acute intra-abdominal disease that necessitated surgical treatment. There had been nausea but no vomiting. There had been no urinary symptoms or chills.

Immediately after the patient entered the hospital, examination revealed a well nourished, healthy looking young man apparently suffering considerable pain. His temperature was 99 F. by mouth; his pulse good and its rate 104 per minute, and his respirations were 24 per minute. Physical examination gave essentially negative results, except for the abdomen, which was slightly tender throughout and quite rigid. The rigidity was boardlike in character throughout, though a little more marked on the right side than the left. All muscle and tendon reflexes were normal. The leukocytes numbered 10,200, and examination of the urine revealed no abnormality. Four hours later the patient's temperature was 100 F. by mouth, and the leukocytes numbered 13,500. The pulse was of good quality, and its rate was only 70 per minute. In spite of the failure to elicit the history of a spider bite, I made the diagnosis of arachnidism and advised symptomatic treatment rather than the exploratory laparotomy which had been previously considered.

The patient's subsequent course proved the wisdom of this decision, for his symptoms gradually subsided and the next day he was sufficiently well and comfortable to go home. At that time his leukocytes and temperature were normal. Some days later his local physician reported that the man was entirely well and apparently none the worse for his experience.

Case 3.—N. E. D., a white man, aged 55, the father of T. D. (case 2), was admitted to the surgical ward service of the University of Virginia Hospital on Sept. 29, 1931, at 9:00 p. m. He complained of pain in his abdomen, legs and back of about twelve hours' duration. At 7:00 a. m. he had gone to the same outhouse toilet as that visited a week previously by T. D. (case 2), and while there felt a sharp, needle-like sting on the right side of his scrotum. He had not seen what stung him and had not given the incident any further consideration. About two hours later, however, he had felt pains in both knees which had radiated up the thighs and localized in the abdomen and back. The abdominal pain had been quite severe and accompanied by nausea and vomiting. He had been most comfortable when lying down with the thighs flexed on his abdomen. During the day the pain had increased in severity, and he had called a physician to see him. The physician, who was not the same one who had attended his son, sent him to the hospital for surgical consideration.

Examination revealed a well nourished, elderly-looking man apparently suffering considerably. His temperature was 101 F. by mouth, the pulse rate 80 and the respiratory rate 24 per minute. His systolic blood pressure was 140 and the diastolic 75 mm. of mercury. The only abnormal physical findings were a small erythematous spot about 1 cm. in diameter on the right side of the scrotum and slight tenderness throughout the abdomen with very marked rigidity of the abdominal muscles. His leukocytes numbered 16,200, but urinalysis revealed no abnormal findings. The intern house officer who admitted the patient to the hospital made the diagnosis of "arachnidism."

The patient improved rapidly, though he suffered from a rather severe and persistent headache. All his symptoms disappeared so that he was able to go home thirty-six hours after the time of his admission to the hospital.

CASE 4.—W. H., a Negro, aged 31, was admitted to the surgical ward service of the University of Virginia Hospital on Oct. 12, 1931. He complained of severe pain in his abdomen of about twelve hours' duration. His symptoms, signs and physical and laboratory findings did not differ in any essential respect from those recounted in the first three cases, except that he had seen and felt a spider bite him. During the night he had visited an outhouse toilet, and just taken his seat when he felt a sharp sting on the foreskin of the right side of the penis. He had a flashlight with him, and when he illuminated the painful area he saw "a black spider with long legs and red spots on his body" clinging to the skin. The abdominal pain had commenced an hour or two after the spider bite had occurred.

CASE 5.—E. B., a white youth, aged 18, was admitted to the medical ward service of the University of Virginia Hospital on Nov. 18, 1931. He complained of severe abdominal pain of seven hours' duration. He had been awakened at 5 a. m. by the pain and had no knowledge of a previous insect bite. All the features of this case were practically identical with those of the previous four cases so they will not be detailed further.

CASE 6.—J. L. G., a white man, aged 35, was admitted to the medical ward service of the University of Virginia Hospital on Nov. 25, 1931. He complained of extremely severe cramplike pain in the abdomen of ten hours' duration. About an hour before the onset of the pain he had felt a sting of some sort on the right wrist while loading rocks on a wagon from a rock pile. The symptoms and abnormal findings characteristic of the previous five cases were found in this instance too, so that the details will not be repeated.

COMMENT

The most striking feature of all the cases was the relative ease with which the correct diagnosis could be made, even without the history of the bite of a spider, if the condition were borne in mind, but likewise the ease with which the mistaken diagnosis of an acute surgical intra-abdominal disease such as perforated peptic ulcer might be made if one were not familiar with the symptoms and signs of arachnidism.

The outstanding symptom in each case was the severe and usually cramplike abdominal pain, while the most prominent physical abnormality was the extreme boardlike rigidity of the abdominal musculature. Regarding the pain in the abdomen, it is important to note that in most of the cases there was an associated pain or ache in the muscles of the thighs or the back. Concerning the rigidity of the abdominal muscles, it is important to note that the tenderness was much less marked than that usually accompanying the rigid abdomen of a perforated peptic ulcer or appendix.

Arachnidism is characterized by the acute onset of severe pain within from a few minutes to an hour or more after the bite of a spider has occurred. Not infrequently the patient is not conscious of having been bitten at all. The characteristic progress of the pain from the site of the bite to the abdomen is often overshadowed by the severity of the abdominal pain and ignored or forgotten by the patient. The pain may actually commence in the abdomen and remain localized there, though in such a

case it usually does radiate to the back or down the thighs, especially during the subsidence of the most acute symptoms. Nausea and vomiting frequently occur. There is characteristically an elevation of the patient's temperature to from 99 to 101 F. with an accompanying leukocytosis of from 12,000 to 20,000. The patient's pulse rate is usually elevated slightly, but in two of the cases of this series it was lower than normal. The blood pressure is usually elevated. Apparently, rigidity of the abdominal muscles, usually boardlike in character, is present in all cases. Palpation, however, reveals less tenderness than would be expected to accompany the rigidity. Morphine administered by hypodermic injection will relieve the pain partially though not entirely, but the rigidity of the abdominal muscles will not disappear after its use.

This summary of the syndrome shows how closely it may simulate an acute abdominal disease necessitating immediate surgical intervention. At a recent meeting of one of the prominent national surgical societies, a paper dealing with acute abdominal disease was read. During the discussion of the paper, a well known surgeon [2] mentioned a group of cases that he said always puzzled him greatly. He described two cases as typical examples. In each of them the symptoms, signs and laboratory findings were similar to those of arachnidism. In each instance the abdomen had been explored but nothing abnormal found except for an apparent spasm of the entire intestinal tract. For lack of a more satisfactory explanation he had ascribed the symptoms and signs to "enterospasm" of unknown origin. In some subsequent cases he had found that the administration of atropine hypodermically would relieve the symptoms. This was learned too late to try it in any of the cases of arachnidism of this report. Dr. Bryan has subsequently told me that he believes arachnidism to be very unlikely as the cause of the acute abdominal symptoms in at least some of his cases of "enterospasm."

While arachnidism has been discussed frequently and many cases have been recorded in the literature, I have found no reference to the syndrome in textbooks or periodicals devoted to surgery. In many of the recorded cases, however, the patient has been subjected to operation under a mistaken diagnosis.

A very comprehensive review of the literature was made by Bogen [3] in 1926. He added fifteen cases to those already reported and made several interesting observations. Apparently the age and sex incidence is unlimited. Some patients came from large cities while others dwelt in the country. Most of the bites occurred in the evening or early morning in the summer or early autumn.

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2. Bryan, W. A.: Personal communication.
3. Bogen, Emil: Arachnidism: Spider Poisoning, Arch. Int. Med. **38**:623 (Nov.) 1926.

Bogen stated that the Latrodectus mactans, frequently called the "black widow," is the chief and perhaps the only really poisonous spider in the United States. It has been found in almost all sections of the United States.

The following description is taken from his article:

Latrodectus Mactans is a shiny, coal black spider, usually brilliantly marked with red or yellow or both. The female, which is always the one responsible
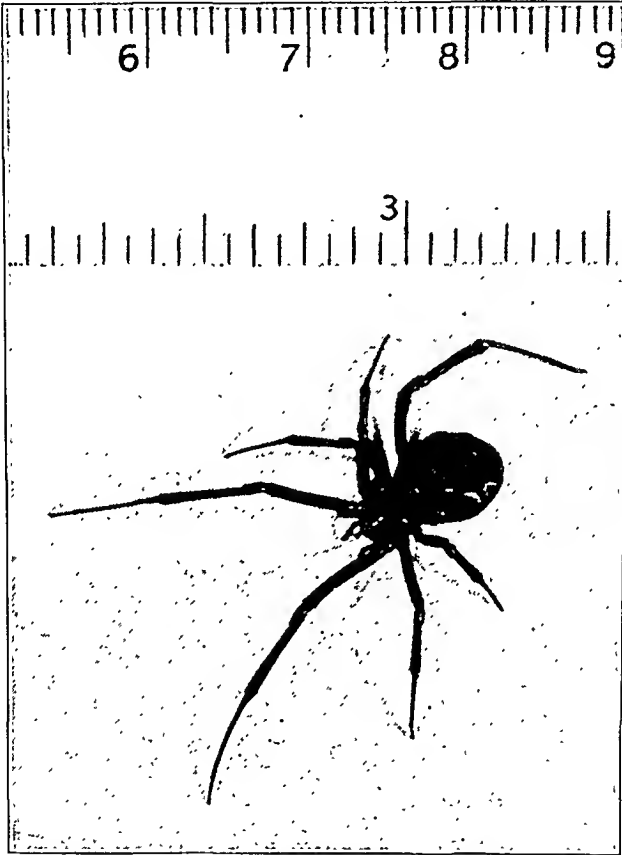

Fig. 1.—Female Latrodectus mactans caught beneath kitchen porch overhanging outside stairs to basement, Charlottesville, Va. (Hindmost left leg is missing.)

for the bites reported, is often a half inch in length when fully grown, and may stretch its slim, glossy, black legs over as much as 2 inches (5 cm.) [fig. 1]. The markings vary greatly, the most constant being a bright red patch shaped somewhat like an hourglass, on the ventral surface of the abdomen [fig. 2]. The globose abdomen, much larger than the cephalothorax, resembles a black shoe button, although it may have one or more red spots along the middle of the back and over the spinnerts, in addition to the ventral patch [fig. 3]. The male is much smaller than the female and is even more conspicuously marked, having four stripes along each side of the abdomen, in addition to the marks of the
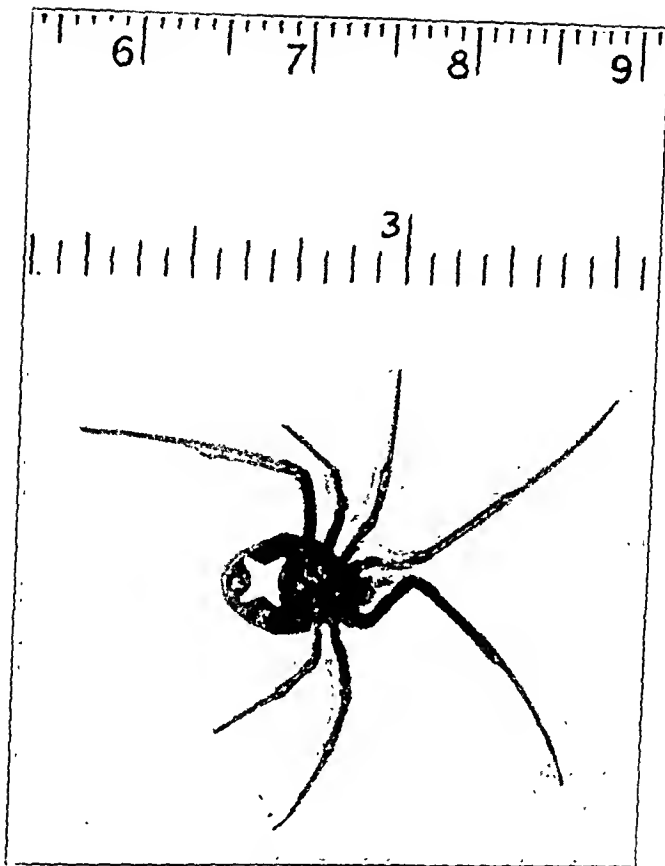
Fig. 2.—Female Latrodectus mactans, ventral aspect, showing "hour-glass," scarlet marking. (Outlined in white for clearer depiction.)

Fig. 3.—Female Latrodectus mactans, showing scarlet spot just cephalad to the spinnerts. (Outlined in white for clearer depiction.)

female. The young spiders are much lighter in color, gradually donning the glossy, black coat in a series of moults over about forty days.

The black widow, as it is called from its custom of eating its mate, is usually found alone, as it will engage in mortal combat with any other spider placed near it. It builds a coarse and irregular dark web in dimly lighted places where it may be undisturbed. Occasionally it is found under stones or pieces of wood or in holes in the ground, in old stumps or bushes, more often in the rafters and corners of little used buildings, in the basements and attics of unfrequented houses, and in the dark corners of barns and other outbuildings, and it has been frequently seen in outdoor toilets, where it builds its web across the seat of the toilet.

More than 150 cases of poisonous spider bites have been reported by thirty-three physicians in the United States during the last century. In several instances the patient was operated on by mistake for an acute appendicitis or other acute surgical abdominal disease, while biliary or renal colic, acute pancreatitis, ruptured gastric ulcer and various forms of poisoning were suggested in others.

Bogen, whose bibliography included 462 references, concluded that "arachnidism or spider bite poisoning is a true clinical entity in the field of general medicine." I might add that this clinical entity may be important to consider in the differential diagnosis of acute surgical abdominal disease.

SUMMARY

Six cases of arachnidism, poisoning from the bite of the Latrodectus mactans, or "black widow" spider, were reported. In some instances the spider bite had occurred without the patient's knowledge. The cases were characterized by the acute onset of very severe abdominal pain, usually nausea and vomiting, boardlike rigidity of the abdominal muscles with more or less tenderness and elevation in the patient's temperature and leukocytes. Attention was called to the ease with which the mistaken diagnosis of acute surgical abdominal disease might be made and the patient subjected to an unnecessary exploratory laparotomy. A previous comprehensive review of the literature by Bogen was briefly alluded to, including his statistics of the incidence of the disease and his description of the spider and its habitat. The importance of arachnidism as a clinical entity to be considered in the differential diagnosis of acute surgical abdominal disease was stressed.

LIGATION OF THE SAPHENOUS VEIN

A REPORT ON TWO HUNDRED AMBULATORY OPERATIONS

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AND

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PREVIOUS LITERATURE

In a previous communication one of us (Dr. de Takáts [1]) advocated ligation of the saphenous vein for certain types of patients afflicted with varicose veins. The operation was described as an ambulatory procedure to be used in combination with injection treatment. Since that time we have been able to perform this operation on one hundred and fifty more patients, and are now presenting a report on the total of two hundred cases, describing the indications and contraindications, the statistical data of our material, the technic, postoperative course and complications and the results and recurrences.

Celsus,[2] in his books on medicine, described an operation for varicose veins as follows:

The skin over the vein being incised, the edges are taken up by a small hook and the vein is drawn apart on all sides from the body; and it is guarded against lest among these things themselves, it may be injured. And a blunted little hook is placed under, and about the same space being placed between (four fingers), the same is done in the same vein; whither it may tend is known easily, the little hook being extended. When the same has been done in whatever part varices are, the vein being drawn in one place by a little hook, is cut off; afterward in what part the next hook is, it is drawn and pulled out and there again is cut off. And thus on all sides the leg being freed from varices, then the edges of the wounds are closed together and an agglutinating plaster is cast on over.

Obviously, multiple excision of small segments of vein were made, but no mention is made of cautery or ligature to stop bleeding. Interesting notes about the etiology and operative treatment of veins are found in Ambroise Paré's work, published in 1579:

The matter of them is usually melancholy blood, for varices often grow in men of melancholy temper and which usually feed on grosse meats or such as breed

1. de Takáts, Géza: Ambulatory Ligation of the Saphenous Vein, J. A. M. A. 94:1194 (April 19) 1930.

2. Celsus, A. C.: De medicina libri octo, Lugduni, Apud J. Tornæsium & G. Gazeium, 1554, book 7, par. 31.

grosse and melancholy humours. Also women with child are commonly troubled with them by reason of the keeping together of their suppressed menstrual evacuation. It is best not to meddle with such as are inveterate; for of such being cured there is to be feared a reflux of the melancholy blood to the noble parts, whence there may be imminent danger of maligne ulcers, a cancer, madnesse or suffocation.

Paré advocated tying the vein below the knee. The last two complications suggest a frequent occurrence of sepsis and pulmonary embolism, although the idea that the varicose blood was dangerous had already been expressed by Hippocrates. The formation of varicose veins was thought to be an effort of nature to sidetrack the deleterious humors that might otherwise cause madness, etc. This opinion was handed on intact until the discovery of circulation.

W. Turner Warwick[3] gave an excellent description of the gradual evolution of the mechanical theory as opposed to the humoral theory of Hippocrates. The mechanical theory of varicose veins was the consequence of Harvey's theory of circulation, and the importance of valves was gradually recognized.

So far as can be ascertained, Home[4] in 1801 practiced ligation of the saphena magna at the level of the knee, with the view of cutting off the column of blood from ulcers. "Within a few hours after the vena saphena has been taken up the symptoms disappear and the patient is led to take notice of the distress it before gave him and to explain the sense of the suddenness of its removal." The operation was condemned because of the frequent occurrence of sepsis. Brodie, cited by Warwick[2] in his lectures on "Surgery and Pathology," appreciated the value of Home's procedure, but he tried other measures of interrupting the continuity of the vein. He tried open division with a compress, whereas Colles devised a vein truss, and Velpeau a pin which passed underneath the vein with the two ends tied together above it.

This was the status of vein ligation when Trendelenburg,[5] in an aseptic era, revived the theory of reflux and established the operation on a rational basis, stating that the vena cava, the iliac vein and the trunk of the femoral vein below Poupart's ligament usually have no valves, and that if the saphenous valves become incompetent a single wide tubular system exists from the heart to the ankle. He also pointed out that the variations of intra-abdominal pressure would be trans-

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3. Warwick, W. Turner: The Rational Treatment of Varicose Veins, and Varicocele, London, Faber & Faber, Ltd., 1931.

4. Home, Everard: Ulcers on the Legs, London, W. Buhmer & Company, 1801.

5. Trendelenburg, Friedrich: Ueber die Unterbindung der Vena saphena magna bei Unterschenkelvarizen. Beitr. z. klin. Chir. 7:195, 1891.

mitted to the saphenous system. To protect this system, he advised saphenous ligature about 3 inches (7.6 cm.) above the knee. Later Perthes, from his clinic, emphasized high ligation at the saphenofemoral junction, as in seven of the seventy-eight cases collaterals developed above the ligature.

The end-results of Trendelenburg's operation were not encouraging. There were from 22 to 72 per cent recurrences reported,[1] so that the method, practiced alone, fell gradually into disrepute. In addition, the percentage of fatal embolism following this operation was estimated from a large personal series of Bernsten as 0.7 per cent. This astonishingly high percentage of embolism has kept many surgeons in constant fear of vein ligations. In reading the description of Trendelenburg's operation, we find that following vein ligation, the patient's legs are bandaged from the ankle to the site of ligature, and are splinted and immobilized for three weeks. These procedures, we fear, are not the proper measures to combat embolism, but are important factors in producing it.

On analyzing our results with the injection treatment for varicose veins,[6] we found a definite percentage of recurrences, which were due to recanalization of the obliterated veins because of an uninterrupted reflux from the proximal segments of the saphenous vein. Therefore, ligation of the saphenous vein was introduced as an adjunct to the injection treatment, preventing backflow, serving as a barricade to ascending phlebitis and reducing materially the number of necessary injections.[1] The combination of injection treatment with vein ligation was not new; Tavel,[7] Schiasis[7] and Moszkovicz[8] advised such a procedure. However, no emphasis has been laid on the importance of the ambulatory type of ligation. Aside from the economic aspect of saving the patient hospital expenses and permitting him to continue work after two days, we hope that the danger of embolism may be obviated or reduced to a minimum in the ambulatory patient.

No smaller authority than Theodor Kocher[9] had his patients get up the second day after a high saphenous ligation, which he combined with multiple percutaneous ligatures of Schede; sometimes as many as two hundred ligatures were employed on one patient. Such patients were allowed to get up the second day and were discharged on the

6. de Takáts, Géza, and Quint, Harold: The Injection Treatment of Varicose Veins, Surg., Gynec. & Obst. **50**:545 (March) 1930.

7. Cited by Sicard, J., and Gaugier, L.: Le traitement des varices par la méthode sclérosante, Paris, Masson & Cie, 1927.

8. Moszkovicz, Ludwig: Behandlung der Krampfadern mit Zuckerinjektionen kombiniert mit Venenligatur, Zentralbl. f. Chir. **54**:1732 (July 9) 1927.

9. Kocher, Theodor: Vereinfachung der operativen Behandlung der Varizen, Deutsche Ztschr. f. Chir. **138**:113 (Nov. 1) 1916.

fifth day. In our series not one patient, whether a dispensary or a private patient, has been hospitalized, and in the two hundred patients we have not observed a single embolism or pulmonary infarct.

INDICATIONS AND CONTRAINDICATIONS

The preliminary report has already stated[1] that when the long saphenous vein is visible or palpable above the lower third of the thigh, the ligature is preferred to injections at this level. It is, of course, possible to make injections into the saphenous vein above this point or even just below Poupart's ligament and produce an obliteration of the vein, but there are several reasons why to us an aseptic ligature seems more advisable in such cases. First, injections are sometimes impossible above the middle of the thigh, because the vein dips deeper and deeper in the subcutaneous fat and may not be palpable at all in spite of existing valvular incompetence. In such patients, if injections are made at a lower level, an ascending thrombosis will make the previously unrecognizable vein suddenly manifest and palpable to the saphenofemoral junction. This progressive, ascending thrombus has none of the characteristics of the thrombus produced at the site of local intimal irritation. It is a stagnation thrombus (static thrombus of Aschoff), and is soft, friable and hardly adherent to the wall. Given the other possibility, that the vein is widely patent to its junction with the femoral vein and injections can be made into it, clots of formidable size, which have been seen to attain 5 cm. in width (fig. 1) cannot be regarded as harmless. The frequently expressed idea of McPheeters,[10] that embolism is not to be feared because of the reversed flow of blood in the varicose vein, refers only to the upright position; certainly in the horizontal position the pressure in the veins of the extremities is negative.

An equally important reason for advocating ligature of the saphenous vein at high levels is frequent canalization of thrombi if the backpressure of blood is permitted to persist. It was with the idea of diminishing the incidence of recurrences that the ambulatory vein ligation was proposed. The backpressure in previous measurements was as high as 210 cm. of water.[11] Our idea has been corroborated and extended by convincing histologic evidence through the significant work of Howard, Jackson and Mahon.[12] They reported the strikingly high

10. McPheeters, H. O.: Varicose Veins, ed. 3, Philadelphia, F. A. Davis Company, 1931, p. 71.

11. de Takáts, Géza; Quint, H.; Tillotson, I. T., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, Arch. Surg. **18**:671 (Feb.) 1929.

12. Howard, M. J.; Jackson, C. R., and Mahon, E. J.: Recurrence of Varicose Veins Following Injection: A Study of the Pathologic Nature of the Recurrence and a Critical Survey of the Injection Method, Arch. Surg. **22**:353 (March) 1931.

incidence of 79 per cent recurrences caused by recanalization. That a totally occluding superficial thrombophlebitis may result in a recanalization of the vein has been seen in five personally observed cases. The double ligature with excision of a segment of at least 3 cm. in length is a permanent block, although a possibility of a "detour" will be discussed later.

In the first communication it has also been stated that the average number of necessary injections following ligation could be reduced from twenty-one to six. The same observation could be made in the present larger series.

Another indication for tying the saphenous vein has been an ascending thrombosis of a spontaneous phlebitis if one is able to ligate above the thrombosis. We have recognized this indication in five cases of acute ascending thrombophlebitis. The ligature not only acts as a barrier to the distal clot, but seems to alleviate the pain by removing the tension of backpressure from the inflamed vessel. These patients have not been strictly ambulatory, as they have been admitted to the hospital and kept in bed for a few days. However, as soon as the fever and pain subsided, they were allowed to get up, and they were home on the fourth day. In addition, other measures were used to hasten absorption of the periphlebitic exudate, the discussion of which is not within the scope of this paper.

The contraindications to ligation of the saphenous vein are few and definite. In the first place, if the venous dilatations are present only below the knee and the long saphenous vein is not palpable even at the level of the inner condyle, the operation is not necessary. Secondly, if there are multiple incompetent anastomoses between the deep and the superficial system, a high ligature of the saphenous vein will not prevent the inflow from the deep veins. In such patients an attempt may be made to make multiple ligations of the incompetent anastomoses. For such multiple ligations we prefer to admit the patient to the hospital for twenty-four hours, just for his comfort, but not with the idea of immobilizing him for any length of time. If there are too many incompetent valves, a high ligation followed by excision and stripping is our method of choice.[6]

Thirdly, the vein ligation is not indicated if a deep venous block is present. Men of great experience in this line, such as McPheeters, have stated that they have never seen a lack of patency in the deep vein. It is, of course, well known that a clot in the deep veins becomes permeable after a certain length of time either by a true canalization of the thrombus or by a reestablishment of circulation through short collaterals and the vasa vasorum. Nevertheless, following a deep venous thrombosis, a certain degree of venous insufficiency persists,

and the ligature of a compensatory dilatation does not seem logical. It may not aggravate the edema, but it will hasten the development of other collaterals. One must also consider the effect of old canalized thrombi on the important femoral valve at the level of Poupart's ligament, which protects the limb from backpressure.

G. P., aged 46, had a left-sided deep thrombophlebitis following childbirth. Twenty-six years later she was seen with a tortuous long saphenous vein, into which a large anterolateral branch emptied. The Trendelenburg test gave a positive result. The Perthes test showed deep patency. There was no edema. A high ligation of the saphenous vein was performed, and multiple injections were made into the thigh and calf distally to the ligation. The patient made an uneventful recovery; at the time of her discharge all the veins were obliterated. There was no edema. One month later, the vein into which injections were made was firmly obliterated, but a new large channel was visible, running parallel with the original vein. The vein started from above Poupart's ligament and was obviously not an overlooked saphenous branch. We have interpreted this recurrence as the result of increased venous pressure in the deep veins, which opened up new superficial veins.

To sum up, then, ligation of the saphenous vein is indicated: (1) in valvular incompetence of the long saphenous vein above the lower third of the thigh, (2) in valvular incompetence of the anastomotic branches, if they resist injection treatment and (3) in ascending thrombophlebitis of the saphenous vein.

The operation is contraindicated: (1) when the vein is not involved above the knee, (2) when there are multiple incompetent valves in the communicating branches which cannot all be ligated and (3) when there is evidence of insufficient deep venous return owing to an old deep phlebitis or a deep valvular insufficiency.

TECHNIC OF AMBULATORY VEIN LIGATION

It would hardly seem necessary to describe a simple vein ligation in detail. Nevertheless, there are a few minor details that are significant because the operation is performed on ambulatory patients. The operations were done in a sterile operating room either at the hospital or in a perfectly equipped operating room of the surgical dispensary, with all necessary precautions such as masks and mouth pieces covering the nose. In the standing position the course of the vein is marked out with a 2 per cent solution of brilliant green. The skin is shaved dry just before the operation and prepared with ether, iodine and alcohol. The line of incision in high saphenous ligations runs about a handwidth distally and parallel to Poupart's ligament and should start mesially to the palpable femoral artery. Naturally, if the vein is palpable at this level, a shorter incision of from 3 to 4 cm. is sufficient. Generally we prefer transverse incisions, because thus some of the accessory saphenous branches are caught and tied. However, if a

longer segment of vein should be excised with its insufficient anastomotic branch, a longitudinal incision is more useful.

The line of incision is infiltrated with 0.5 per cent procaine hydrochloride with 3 drops of 1 : 1,000 epinephrine to each ounce (fig. 1). Only a superficial subcutaneous infiltration is made, and repeated aspirations are made for blood. Because of the vicinity of the large vein, care must be taken not to inject any procaine hydrochloride intravenously. In one patient, as reported in our previous article,[1] only a few drops of procaine hydrochloride were sufficient to produce pallor, tachycardia and numbness of the lips and fingers. The toxic effects wore off in a few minutes, but illustrate the necessity of extreme care in this region to avoid intravenous injection.
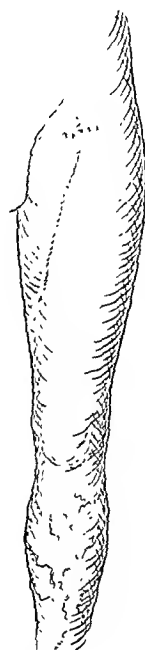

Figure 1   Figure 2

Fig. 1.—Ligation of the right internal saphenous vein. A week later a massive clot was palpated above the knee. The left side has not been treated.

Fig. 2.—The course of the vein is outlined in the standing position at the highest palpable point with a 2 per cent aqueous solution of brilliant green. Five-tenths per cent procaine hydrochloride solution with 3 drops of epinephrine, 1 : 1,000, is used to infiltrate a transverse line of incision. Beware of intravenous injection!

After waiting about five minutes for a complete anesthesia, incision is made through the skin and subcutaneous fat. In some patients a strong tortuous anterior branch lies immediately under the skin and needs no further exposure. This, however, may not be the main trunk, but a collateral from the superficial epigastric, overcoming a previous iliac block. At this high level (three fingerbreadths below Poupart's ligament) the main trunk lies below the superficial fascia and has to be exposed at a depth of from 2 to 4 cm., or sometimes even more. When the main vein is exposed, a perivenous injection is made on both sides of the vein as traction on the perivenous sympathetic fibers produces pain (fig. 2). A curved artery forceps

or aneurysm needle armed with no. 1 chromic catgut is insinuated under the vein twice (fig. 3). The two ligations are tied at a distance of 3 cm. or more, and the segment of vein is well·lifted up to detect communicating branches from the deep veins, which should also be carefully tied as they may produce a profuse hemorrhage (fig. 4). It is important to place the proximal ligature as close to the femoral junction as possible, leaving a very short stump. As an added precaution a second ligature may be applied to the proximal stump, as considerable pressure is exerted on it in the ambulatory patient.

The segment of vein is then removed, and it is used for bacteriologic study. Before the wound is closed the patient is asked to cough a few times to catch, if
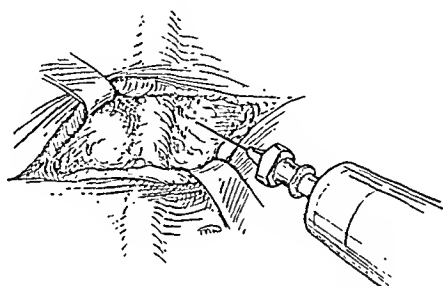

Fig. 3.—A short transverse incision is made through the skin, the subcutaneous fat and, if necessary, the superficial fascia. When the vein is exposed, a few drops of procaine hydrochloride are injected around it.
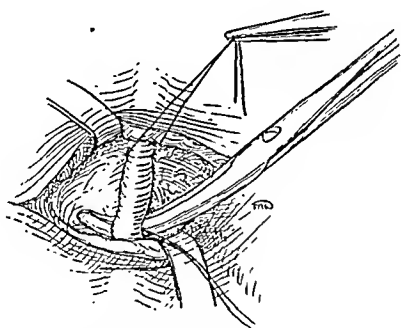

Fig. 4.—A curved artery forceps, carrying a number 1 chromic catgut ligature, is passed under the vein. The vein is lifted up, and another ligature is placed at least 1 inch proximal to the first one. The proximal ligature should be close to the saphenofemoral junction.

necessary, additional bleeders. No sutures are placed in the subcutaneous fat, and the skin is closed with interrupted dermal sutures. The skin around the incision is now painted with a mastic solution,[13] and the gauze is stuck to the skin with the solution (fig. 5). In ambulatory patients who perspire freely, sweat and dirt cannot be kept away from the incision with the usual adhesive tape bandage. This solution, which one of us has used exclusively since 1914 in all aseptic operations, keeps the skin around the incision dry and protected. We strongly emphasize its

13. Gum mastic, 40 Gm., benzene, 60 cc., castor oil, 20 drops; then add sufficient M. Sc. **184**:57 (July) 1932.

use here, particularly in dispensary patients, who sometimes return with soiled and slipped dressings.

The patients return for inspection in forty-eight hours, and the stitches are removed on the eighth day. They are asked to stay away from work for the first two days and may return to work after the first inspection. They should not stay in bed during the day for any time.
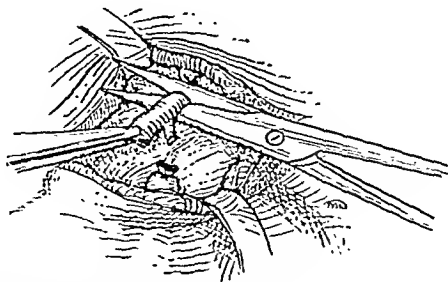

Fig. 5.—Both ligatures are tied. The segment of vein between the two ligatures is excised. No clamps are used at any time.
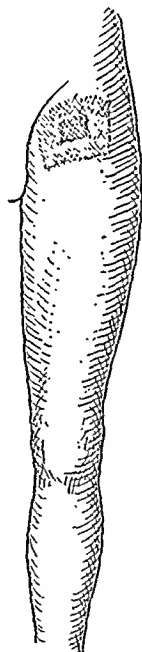

Fig. 6.—The bleeding is accurately controlled. Interrupted dermal sutures approximate the edges of the skin. The skin around the line of suture is painted with a solution of mastic in benzene, and a layer of gauze is stuck to the skin, which produces a water-tight dressing. Elastic compression is applied on top.

ANALYSIS OF MATERIAL

Age, Sex and Previous Treatment.—This report is based on two hundred ambulatory vein ligations, performed on dispensary patients [14]

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14. The operations were performed by Drs. Zimmermann, Jacques, Quillin and Quint, members of the Varicose Vein Clinic.

and in the private practice of the authors. The patients' ages, classified in decades, were as follows:

Decades	Number of Patients
10–20	2
20–30	30
30–40	69
40–50	58
50–60	34
60–70	5
70–80	2
	200

Ninety-five per cent of the patients were between 20 and 60 years of age, 1 per cent between 10 and 20 and 1 per cent between 70 and 80.

There were ninety-four female and one hundred and six male patients, illustrating, as has been pointed out before, that at least in our material there is no feminine prevalence.

As to occupation, all walks of life are represented, the majority of cases occurring in patients giving a history of long hours on their feet or hard manual labor in the upright position.

The influence of heredity, studied in a previous report,[6] was again very striking. Particularly significant seems the observation that whenever varicose veins are encountered in the young both parents were affected.

The previous treatment of these patients was as follows:

140	Had had no previous treatment
3	·Had had surgical excisions (but no high ligation)
8	Had worn Unna's casts
49	Had had injection treatment
200	

Of the three surgical excisions, not one could be called radical, judging from the scars. The saphenous vein was not ligated below Poupart's ligament, and short scars were present on the calf and thigh. In the eight cases in which Unna's casts had been applied for varicose ulcers elsewhere, the patients were not progressing rapidly and there was a marked reflux of blood from above. Of greatest interest are the patients who had had injection treatment elsewhere or from us. It is this group that made us realize that the number of recurrences, reported elsewhere as 10 per cent, should be reduced by ligation. These patients fall into two groups: one in which obliteration was never accomplished (in one case as high as fifty injections were given) and another in which early recanalization took place. In the private practice of one of us, ligations in patients who had previously been given

injections became necessary seven times because of repeated recurrences. Since the ligations, recanalization has not occurred in this group.

The postoperative disability was estimated as follows (all patients were told to take one day off following the operation) :

Number of Patients	Disability
161	None
22	1 day
8	2 days
3	3 days
3	4 days
1	8 days
1	9 days
199	

An analysis of patients who were disabled for more than two days will be made in the section on complications.

Complications.—One patient had a hemorrhage owing to the slipping of the proximal ligature. She was taken to a hospital, where the hemorrhage was controlled. The patient made an uneventful recovery. In one patient a hematoma developed, which produced a serous discharge for nine days and then healed up completely. In one patient a wound infection developed on the fourth day; the abscess was opened. The patient was not hospitalized, and the wound healed in eleven days.

One patient died of streptococcic septicemia. A wound infection developed in this patient, which was obvious on the fourth day, but for various reasons the patient could be hospitalized only on the tenth day, when he was admitted with a generalized streptococcic septicemia. Death occurred as a result of the infection. At autopsy no thrombosis of the proximal saphenous stump or of the femoral vein was found. Death occurred because of a surgical infection, which was localized but because of improper after-care resulted in a generalized infection.

One patient, whose case was reported in our previous series, had a slight procaine hydrochloride reaction during the operation owing to an intravenous injection of the drug. The toxic symptoms disappeared within a few minutes.

A tabulation of complications shows the following:

Procaine hydrochloride reaction	1
Hematoma	1
Postoperative hemorrhage	1
Wound infection	1
Death from septicemia	1

We believe that all of these complications are preventable, at least to a minimum. They have not occurred in our private work. The

procaine hydrochloride reactions will not be encountered if frequent, careful aspirations are made for blood before the drug is injected. Hematomas can be reduced to a minimum if all tributaries are carefully tied, if the patient is asked to cough or strain before closing the wound and if a tight pressure bandage is applied. Slipping of the proximal ligature occurred once; since that time, a double ligature has been placed on the proximal stump. Care must be exercised to leave a large enough segment of the vein distal to the ligature. The one death from septicemia was due to an initial surgical infection, which unfortunately still occurs in any large group of aseptic operations. It is probably unavoidable at the present time, although all operations were carried out under strict aseptic precautions, with masked head, nose and · mouth. The measures that should be carried out, however, in all cases showing infection consist in immediate hospitalization, immobilization and hot wet dressings, with incisions when necessary.

Secondary infection from the skin in these ambulatory patients is also a possibility. We strongly emphasize the use of the glue, the mastic solution, which forms a watertight contact between the skin and dressing and prevents perspiration.

Thrombosis Following Vein Ligation.—Of the two hundred patients, sixty-five, an incidence of 32.5 per cent, showed a massive thrombosis distal to the ligature. Of this group, forty, that is, 20 per cent of the original two hundred, showed complete obliteration, which did not necessitate further injections. It seems obvious that it is in this group of patients who are cured after Trendelenburg's vein ligation, although none of the older statistics bring out this point, that the patients who have a distal thrombosis following the operation are the ones who remain cured. It is because of the comparatively frequent occurrence of distal thrombosis that we do not advocate injections at the time of ligation, as they may not be necessary or they may even activate a resting infection.[15]

The thrombosis following ligation may be purely static and aseptic, occurring in the form of a narrow, firm cord, with no inflammatory reaction around it, but more frequently it is accompanied by a massive · periphlebitic exudate, which is hot and tender on pressure but does not lead to an elevation of temperature. Of the eight patients who were disabled more than two days, five belonged to this group. If the patients are given proper elastic support in the form of Unna's paste boot or an elastic adhesive bandage, they are comfortable. They should not be put to bed, but should be encouraged to be up and around, as we think that the ambulatory ligation is our real safeguard against embolism.

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15. de Takáts, Géza: The "Resting Infection" in Varicose Veins, Am. J. M. Sc. **184**:57 (July) 1932.

The thrombosis in the proximal stump is, of course, of even greater interest and has been carefully looked for in every case. The idea of some surgeons, that every vein ligation results in a massive clot proximal to the ligature, cannot be substantiated. If the vein is occluded with a ligature without first crushing it with artery forceps, the endothelial damage is small and nothing but a microscopic clot results. The classic experiment of Baumgarten, who showed that blood did not have to clot in the vein between two ligatures, should be recalled. If one could not tie a vein without the danger of embolism, surgeons would have to cease to operate entirely.

Of the two hundred vein ligations, there was a palpable clot in the proximal stump in eighteen (9 per cent). Occasionally a large varix at the level of Poupart's ligament, obviously above the saphenofemoral junction, would diminish in size or disappear. We have become more and more impressed with the facts, which have already been stressed by Margrit Hanselmann [16] in an inaugural dissertation, that the longer the proximal stump, the more apt is the proximal clot to appear, and that ligation close to the saphenofemoral junction is the best measure to avoid large clots in the proximal stump. Thus, aside from the ambulatory operations, the shortness of the stump is another safeguard against massive embolism.

Of the eighteen patients showing a proximal thrombosis, all but three had a distal thrombosis, which is suggestive of an increased endothelial reactivity of the patients. According to Dietrich, one of the foremost pathologists, the increased susceptibility of the endothelial lining is an important factor in thrombus formation.[17]

Whether it is possible to predict the occurrence of a distal or proximal thrombosis following vein ligation is an open question. Elsewhere one of us described simple methods of detecting resting infection previous to injection treatment.[15] The same procedures, namely, provocative vein puncture, diathermy or roentgen exposure, can be used to diagnose a latent infection or an increased susceptibility of the vein. However, such "flare ups" are much less frequent following ligation than after injections, because a ligature is much less irritating to the vein than an injection.

The occurrence of a proximal clot in 9 per cent of our cases makes one wonder why injections at high points would not be equally satisfactory so long as the ligature also produces a fairly large clot. We

16. Hanselmann, Margrit: Postoperative Thrombose und Embolie und ihre Prophylaxe, Inaug. Diss., Zurich, 1926.

17. Dietrich, A., and Schröder, K.: Abstimmung des Gefässendothels als Grundlage der Thrombenbildung, Virchows Arch. f. path. Anat. 274:425, 1930.

have stated our standpoint in discussing the indications for ligation. The small aseptic clot, the permanent interruption of the venous channel with no chance of recanalization and the possibility of going up within an inch or less of the saphenofemoral junction and catching all branches not only make the operation safer, but also give a better prognosis so far as the end-results are concerned. The statement that the irritative thrombus is safer than the aseptic ligature thrombus because the former is more firmly attached holds only in cases in which the irritative thrombus is aseptic. Since, however, we have shown in our clinic that of fifty-eight clinically uninfected veins more than half gave a positive bacteriologic culture, we hesitate with injections for fear of a progressive thrombosis with inflammatory reaction. That the ligature can be safely applied under such conditions is best shown in patients whose veins have been tied during an acute ascending phlebitis with no reaction in either stump. The course of the five patients whose saphenous veins were tied during an acute attack of ascending superficial phlebitis was so satisfactory that such a procedure must always be considered, without prolonged immobilization.

Results of Vein Ligation.—In the present material a distinction must be made between the dispensary material (one hundred and thirty-five cases) and our private material. Both groups serve to elucidate important points.

The dispensary material contains eighteen patients who had previously been given injections elsewhere or by clinicians in our group, with no results. In these cases a total of two hundred and one treatments have been given with no obliteration, whereas following ligation the patients were discharged as cured after a total of fifty-seven treatments. The cases show such a striking effect of this operation on the right type of patients that we have tabulated the results individually (see the accompanying table). Patients 8 and 13 had partial excisions with stripping of the vein, but no high saphenous ligation. The veins were obliterated in six cases, eight injections being given following ligation. Patient 16 was treated with "many injections" elsewhere, so that the number of treatments is not included in the treatments preceding ligation.

We had originally hoped to present exact follow-up statistics of the entire material of two hundred cases. This was only possible of approximately one third of the dispensary material, although a real effort has been made by our social service department to have the patients appear for reexamination. In the private work of one of us it has been possible to secure exact data in 91 per cent of the cases in which operations were performed. The patients came in every three months for the first year, every six months the second year and

then once a year for the next three years. The first ambulatory vein ligation was performed in 1927; the first patient was under observation for four years.

As the dispensary material could not be adequately controlled for follow-up purposes, we shall limit ourselves to a discussion of the private cases, of which sixty exact records are available.

Of the sixty patients, in five a dilatation developed above the ligature. Four of these patients were operated on in 1927 or 1928, when ligatures were placed at the midthigh. Since then we have learned to insist on a high ligation at the saphenofemoral junction. One patient who had had a bilateral high ligation returned with a large dilatation at Poupart's ligament just above the scar, but only on the right side. The only

Results of Vein Ligation Following Unsuccessful Injections

Patient	Number of Unsuccessful Treatments	Number of Treatments After Ligation	Follow-Up Notes*
1	20	6	Complete obliteration
2	2	1	Complete obliteration
3	2	5	No recurrence in 6 months
4	10	0	Total thrombosis
5	5	3	Excellent results; seen after a year
6	6	2	Complete obliteration
7	14	1	Excellent result
8	Vein stripping	0	Complete collapse
9	11	6	No record
10	24	1	Complete obliteration
11	23	4	No recurrence in 4 months
12	2	4	Complete obliteration; ulcers healed
13	Vein stripped	9	Complete obliteration
14	7	2	
15	50	0	Complete thrombosis
16	"Many injections"	0	Complete obliteration
17	20	0	Complete obliteration
18	5	7	Complete obliteration
	201	57	

* The notes were made at least three months after operation. The patients were asked to return every three months for a year.

possible explanation was that this patient's femoral valve was deficient or absent, which fact was corroborated by the unusually strong impulse in this vein following coughing or straining. At reoperation a large, thin-walled, saccular dilatation was found between the proximal ligature and the saphenofemoral junction. This was *completely excised*, the new ligature being placed at the saphenofemoral junction. The exposed femoral vein showed such marked fluctuations to inspiration, coughing or sneezing that the diagnosis of the absence or incompetence of the femoral valve was certain. The significance of this anomaly must be investigated in other cases.

Recurrences caused by a marked reflux through incompetent perforating veins occurred only in two of the sixty patients (3 per cent). We have previously stated [a] that patients with large incompetent communications between the deep and superficial veins must have a radical

excision. Quite recently we have tried to ligate the incompetent perforating branches at the time the high saphenous ligation was done, but we cannot report any end-results at this time.

A summary of the recurrences following vein ligation combined with injections in sixty private cases is as follows:

Dilatations proximal to the ligature (4 low ligations, 1 incompetent
femoral valve) 5
Dilatations distal to the ligation (incompetent perforating veins)..... 2
                                                                    ——
                                                                     7

The final analysis of these recurrences [18] indicates that high ligations should be done in every case, and that either the incompetent perforating veins should be ligated or a radical excision should be made. When one considers, furthermore, that patients who are submitted to vein ligation suffer from the most extensive and progressive type of varicose veins, the end-results show that the combination of vein ligation with injections offers in the suitable type of patient the best chances for permanent results.

Embolism Following Vein Ligation.—In the two hundred cases of ambulatory vein ligation we have not encountered any case of pulmonary embolism or ascending deep thrombosis. One cannot state that the operation is entirely free from this risk, because no operation is. We do believe, however, that two factors, namely, the ambulatory management and the shortness of the proximal stump, are important in the prevention of embolism. The classic description of ligation of the saphenous vein, which called for splinting and three weeks' immobilization in bed, showed the alarming percentage of 0.7 per cent of fatal pulmonary embolisms. When statistics will be available of at least one thousand ambulatory vein ligations, some statement may be made as to the frequency of this complication. We have good reason to believe, though, that they will compare favorably with minor ambulatory operations in this respect.

CONCLUSIONS

On the basis of two hundred ambulatory vein ligations combined with the injection treatment for varicose veins, we think that this procedure has a definite place in the treatment for this condition. The high saphenous ligation protects the treated veins from fluctuations

18. These recurrences indicate that when ligation of the saphenous vein combined with injections was done with proper indications and proper technic a recurrence was found in one of sixty cases (0.6 per cent). This one recurrence was due to an incompetent femoral valve, a condition that we have overlooked entirely up to the present time.

of abdominal pressure and hydrostatic pressure, thus preventing canalization of the thrombi. It also reduces the necessary number of injections and places the occluding ligature close to the saphenofemoral junction. By insisting on a short proximal stump and on ambulatory management, we can report no embolism in the entire series. The complications reported in this series all seem avoidable with growing experience. The end-results of the operation combined with injections show a far smaller percentage of recurrences than those obtained with any other procedure in the treatment for varicose veins.

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AVERTIN AS AN ANESTHETIC FOR GENERAL SURGERY

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In order to determine the worth as well as the limitations and dangers of the various new anesthetic agents, it is desirable that reports of many cases from different clinics be made. With this in view I have undertaken a critical analysis of the cases in which avertin was used either as the anesthetic or for basal narcosis supplemented with some form of inhalation anesthesia in the surgical clinic of the University of Michigan Hospital. This statistical survey covers the period from November, 1929 (when avertin was first adopted in this clinic), to January, 1932, and comprises 430 cases. Operations done in the divisions of genito-urinary and orthopedic surgery in which avertin was employed are included, but the cases in the neurosurgical field have been reserved for a separate report. While avertin was not used as a routine measure for any particular type of work, it was employed rather extensively in abdominal operations and also in operations performed on the face or about the mouth. In all of these cases considerable discretion was exercised in the selection of the patients. Ordinarily cachectic or very elderly persons as well as those greatly debilitated from chronic disease were excluded. In such patients the risk of pulmonary complications arising from a prolonged postoperative period of somnolence seemed to be unwarranted, and for them another anesthetic was usually selected.

AGE AND SEX

The age according to decades and the sex incidence of the 430 cases are shown in table 1. The preponderance of men over women is of no significance as it simply reflects the fact that in this clinic there are more male than female surgical patients. While avertin was used fairly often for children, the instance of the patient 83 years old was an exceptional one. The average age of 36.2 years is an interesting figure, since it shows that fairly young and reasonably sound patients made up the majority of the group.

From the Department of Surgery, University of Michigan.

DOSAGE

The dose in milligrams was in all instances calculated according to body weight. Table 2 shows the doses expressed in milligrams per kilogram which were employed. It will be noted that 110 mg. per kilogram was almost our standard dose. This was occasionally increased in some exceptional circumstances, and likewise on some occasions it was reduced. A dose of 110 mg. per kilogram has seemed to be satisfactory and safe, whereas at no time has it been my aim through either

TABLE 1.—*Age and Sex Incidence*

Age by Decades	
1–9	9
10–19	69
20–29	77
30–39	107
40–49	69
50–59	59
60–69	32
70–79	6
80–89	2
Total	430
Youngest patient	4
Oldest patient	83
Average age	36.2 years
Sex	
Males	232=53.9%
Females	198=46.1%

TABLE 2.—*Dose of Avertin*

Mg. per Kg.	Number Cases	Per Cent
130	9	2.08
125	3	0.78
120	24	5.47
115	12	2.86
110	344	79.96
100	25	5.73
90	4	1.04
80	8	1.82
50	1	0.26
Total	430	100

the use of excessive doses of avertin or the use of heavy preoperative medication to produce complete surgical anesthesia without some form of reinforcement. The addition of a supplemental anesthetic such as nitrous oxide and oxygen or ether is without question a safer method. While 110 mg. per kilogram is a somewhat larger dose than that used by many surgeons, it has not seemed objectionable in my hands. When the smaller doses were employed, the *results were considerably* less satisfactory. With regard to children, my experience has been in accord with that of others. i. e., that they are more tolerant to avertin than adults, and even with doses of 110 mg. per kilogram, supplementary anesthesia was required in every case.

ADMINISTRATION

Almost as a routine procedure the patients were narcotized in their own beds in the ward or private room. The general standard technic of administration recommended by the makers of the drug was followed. Cleansing enemas were given in the evening before the day of operation but ordinarily not on the operative day. Occasionally a mild sedative was given on that same evening. Most of the patients received some form of preoperative medication. This consisted for the most part of morphine sulphate, from $\frac{1}{6}$ to $\frac{1}{4}$ grain (11 to 16 mg.), or a mixture of opium alkaloids hydrochlorides, $\frac{1}{3}$ grain (22 mg.). Atropine was usually omitted, while rarely hyosine, from $\frac{1}{150}$ to $\frac{1}{100}$ grain (0.4 to 0.6 mg.), was used in conjunction with morphine. The calculated quantity, ranging approximately from 175 to 300 cc. of the 3 per cent solution of avertin which had previously been prepared by an expert pharmacist and kept at a temperature of 40 C., was administered by a nurse anesthetist. The fluid was introduced into the rectum through an ordinary male catheter with funnel attached and was allowed to flow in slowly by force of gravity. The ease of the induction and the absence of an excitement stage or struggling were noteworthy. The induced sleep seemed to resemble natural sleep more closely that that brought about by any other artificial means. The color of the patient was usually good, and there was an absence of marked sweating. Cyanosis was rarely noted. In from fifteen to thirty minutes the full depth of the narcosis was reached, and at or slightly before this time the patient was transported to the operating room. The transfer to the operating table, the preparation of the skin and the arrangement of drapings were carried out as usual. If cutaneous stimuli provoked a reflex response, a supplemental inhalation anesthetic was started at once. Otherwise, the operation was started and reinforcement resorted to when and if it became necessary.

TYPES OF OPERATION

The various operations that were performed are shown conveniently grouped in table 3. It will be noted that considerable use was made of avertin in operations about the head or in the mouth as well as in the various abdominal operations. In the former type of operation, where gas masks or ether cones are apt to encroach on the operative field and so hamper the operator, an anesthetic substance that can be introduced into the circulation by way of the rectum has outstanding advantages. In the laparotomy group avertin gave important assistance in bringing about the requisite degree of muscular relaxation. The second column of figures in the table is of interest. It designates the number of cases in which no supplemental anesthetic was required and shows that this was chiefly in operations which did not involve opening the peritoneal cavity. It is of some interest that only 5, i. e.. 12.5 per cent. of the

goiter operations (which ordinarily can be done under comparatively light anesthesia) were completed with avertin unassisted. This seems to bear out the observation that hyperthyroidism produces a greater tolerance to avertin, while conversely hypothyroidism is said to render a patient less tolerant and in such cases the dose should be correspondingly reduced. In keeping with this it was also frequently found that in using nitrous oxide and oxygen with avertin the ratio of the gases had to be kept at approximately the same level as in the cases in which no avertin was used.

TABLE 3.—*Operations under Avertin*

Type of Operation	Total Number	Number Performed with Avertin Unassisted
Face and mouth	68	40
Hernia (all varieties)	54	11
Kidney and ureter	47	10
Gallbladder and biliary tract	44	7
Thyroidectomy	40	5
Appendectomy	36	14
Plastic	21	5
Exploratory laparotomy	20	4
Bone and joint	19	5
Resection cervical glands	18	6
Breast	10	4
Miscellaneous	9	5
Gastric resection	9	4
Gastro-enterostomy	7	0
Lumbar sympathectomy	6	1
Bladder and urethra	5	0
Colostomy	4	2
Amputation (thigh or leg)	3	1
Cholecystogastrostomy	2	2
Esophageal diverticulectomy	1	1
Duodenum	2	1
Pericardiotomy	1	1
Gastrostomy	1	1
Splenectomy	1	0
Lobectomy (pulmonary)	1	0
Gastrocolic fistula	1	0
	430	130

SUPPLEMENTARY ANESTHESIA

Table 4 indicates the number of the cases in which supplemental inhalation anesthesia was necessary. As will be noted, nitrous oxide and oxygen was the supplemental anesthetic of choice and was used in the great majority of cases. In 33 cases this alone was not sufficient, and a moderate quantity of ether vapor was given through the McKesson machine. The 21 cases in which ether alone was used for reinforcement call for some comment. These cases were of two types: The first group involved operations done inside of the mouth where anesthetic apparatus was objectionable. In these cases the avertin was supplemented at intervals with ether given through the ether vapor apparatus. The other group was composed of very major abdominal

procedures in which most complete muscular relaxation was necessary, such as lumbar sympathectomy and operations on the biliary tract or deep in the pelvis in muscular persons. A synergistic effect between avertin and ether was noted, and in many cases the ether was necessary only during the preliminary exploration of the abdominal cavity and the packing off process, and could be discontinued during the remainder of the operation with possibly a small quantity again for closure of the peritoneum. Thus the total quantity of ether would range from only ½ to 2 ounces in many of the cases, with nevertheless a high degree of muscular relaxation. When nitrous oxide with oxygen was the supple-

TABLE 4.—*Supplementary Anesthesia*

	Number Cases	Per Cent
None	130	30.23
Gas	246	57.21
Ether	21	4.88
Gas and ether vapor	33	7.68
	430	100

TABLE 5.—*Evaluation of the Anesthetic*

	Number	Per Cent
Good	235	54.64
Satisfactory	64	14.95
Fair	48	11.08
Excellent	42	9.79
Very good	25	5.93
Poor	16	3.61
	430	100

mental anesthetic, the percentage of oxygen in the mixture could usually be considerably increased. The average ratio of the gases used for this entire group was 82 : 18 which, of course, means that the percentage of oxygen is practically double the amount possible when used with nitrous oxide alone. Oftentimes the percentage of the oxygen in the mixture was considerably higher than this, starting with a 90 : 10 ratio of the gases and tapering off to perhaps a 50 : 50 ratio at the conclusion of the operation.

EVALUATION OF THE ANESTHETIC

In table 5 an attempt has been made to evaluate the quality of the anesthesia. At the conclusion of each operation the operating surgeon was requested to state his opinion of the anesthetic for that particular case. The opinions expressed show that in about 86 per cent of the cases the anesthesia was entirely satisfactory, while in slightly less than 14 per cent it was thought to be only fair or poor.

BLOOD PRESSURE CHANGES DURING AVERTIN ANESTHESIA

In the entire number of cases, careful recordings were made of variations in blood pressure, both systolic and diastolic, as well as changes in the pulse and respiration during the course of the operation. In each case a basal blood pressure reading was taken before the administration of the avertin. There was considerable variation in this initial pressure among the different patients, the highest systolic reading being 210 mm. of mercury and the lowest 72, with an average systolic pressure of 120. Of the diastolic recordings, the highest that was noted was 140 and the lowest 20, with an average diastolic pressure of 72. After the administration of the avertin it was ordinarily noticed that there was a moderate decline in pressure during the first fifteen or twenty minutes; the pressure then gradually rose again, and at the conclusion of the operation was approximately at the preoperative level. In most

TABLE 6.—*Stimulants During Operation*

Stimulants	Number	Per Cent
None	360	83.77
Caffeine	47	11.00
Ephedrine	9	2.09
Both.	14	3.14
	430	100
Intravenous dextrose		7
Blood transfusion		5

cases this preliminary drop in blood pressure was not sufficient to cause concern, and there were no attendant objectionable symptoms such as cyanosis or marked changes in the pulse. In case the drop in pressure was extraordinary or tended to be prolonged, it was found that this could be satisfactorily counteracted by the use of ephedrine or epinephrine. In general, it seemed that the administration of some inhalant, such as ether, nitrous oxide or carbon dioxide, aided considerably in bringing up a lowered blood pressure. Table 6 shows the incidence of the use of the various stimulants during the course of the operation. The cases noted in which intravenous dextrose or blood transfusion was required were cases in which the nature of the operation made these expedients necessary, and it was through no possible fault of the anesthetic that they were required. Likewise, the rather large number of cases in which caffeine was given is not a true index of the actual necessity for stimulation consequent on the anesthetic. It was more or less customary at the conclusion of the operation, if the patient was still profoundly narcotized, to administer an ampule of caffeine in order to shorten somewhat the postoperative reaction time. On the whole, my experience would not tend to show that the fall in blood pressure

from the use of avertin was highly objectionable, and it certainly does not seem comparable either in magnitude or as a cause for alarm with the changes in blood pressure that occur during the use of spinal anesthesia. After the administration of the avertin, blood pressure readings were taken at ten minute intervals during the course of the operation. As stated before, the maximum fall in pressure usually occurred from ten to thirty minutes after the introduction of the avertin, and these changes may be summarized as follows: Of the 430 cases followed, in 17, or 4 per cent, there was no initial change in systolic blood pressure. In 357 cases, or 83 per cent, there was a decline in systolic pressure, and in 56 cases, or 13 per cent, there was an actual initial rise in pressure. In the cases showing a decline in systolic pressure the average decrease amounted to —28 mm. of mercury, or a drop of 23 per cent, while

TABLE 7.—*Changes in Blood Pressure*

			Number Cases	Per Cent	Average Amount, Mm. Hg.	Per Cent	Total Average, Mm. Hg.	Per Cent
Systolic	Initial	No change	17	4	....	....		
		Increase...	56	13	+28	+23	—20	—17
		Decrease..	357	83	—28	—23		
	Final	No change	39	9	....	....		
		Increase...	163	38	+ 2	+ 1.7	— 5	— 4
		Decrease..	228	53	— 2	— 1.7		
Diastolic	Initial	No change	34	8	....	....		
		Increase...	91	21	+17	+24	—10	—14
		Decrease..	305	81	—19	—27		
	Final	No change	65	15	....	....		
		Increase...	189	44	+15	+21	+0.3	+0.4
		Decrease..	176	41	—15	—21		

those showing a rise in systolic pressure showed an average increase of + 28 mm. of mercury, or a rise of 23 per cent. The total average initial systolic change amounted to — 20 mm. of mercury, or a drop of 17 per cent. Regarding the initial change in diastolic pressure, of the 430 cases there was no initial change in 34, or 8 per cent. In 305 cases, or 71 per cent, there was a decrease in pressure and in 91, or 21 per cent there was an increase. The amount of these changes is as follows: The average decrease for the 305 cases was — 19 mm. of mercury or a 27 per cent fall, while the average increase in the 91 cases showing an initial rise was + 17 mm. of mercury, or a 24 per cent increase. This gave a total average initial change of — 10 mm. of mercury or a fall of 14 per cent. At the conclusion of the operation the following changes in pressure were noted: Of the 430 cases, the systolic pressure was at the preoperative level in 39, or 9 per cent. In 228, or 53 per cent, it was still below the preoperative level, while in 163 cases, or 38 per cent, it was above the basal reading. Of the cases in which there was a final decrease in systolic pressure, the average

amounted to — 2 mm. of mercury, or 1.7 per cent. Of those show-ing an increase, the average increase was + 2 mm. of mercury, or 1.7 per cent, while the total average systolic change was — 5 mm. of mer-cury, or a 4 per cent drop. Final diastolic changes were as follows: Of the 430 cases, 65, or 15 per cent, showed no change; 176 cases, or 41 per cent, showed a decline and 189 cases, or 44 per cent, showed an increase. Of those showing a decrease, the average decline was — 15 mm. of mercury, or 21 per cent, while the average increase in those showing a rise was + 15 mm. of mercury, or 21 per cent, and the total average diastolic change was negligible. Table 7 summarizes these changes in blood pressure.

CHANGES IN PULSE AND RESPIRATION

Changes in the pulse rate following the administration of avertin were also studied. Of the 430 cases, 30, or 7 per cent, showed no

TABLE 8.—*Changes in Pulse and Respiration*

		Number Cases	Per Cent	Average Number Beats	Total Average
Pulse	Increase..............	262	61	+19	+7
	Decrease..............	138	32	—16	
	No change............	30	7	....	
Respiration	Increase..............	305	71	+ 9	+6
	Decrease..............	60	14	— 4	
	No change............	65	15	....	

change in pulse rate after the administration; 138 cases, or 32 per cent, showed a decrease in the pulse rate, while 262, or 61 per cent, showed an increase. The average increase in those showing an elevation in pulse rate was + 19. The average decrease in those showing a drop was — 16, while the total average pulse change was + 7. The changes in respirations were: Three hundred and five cases, 71 per cent, showed an increase in the respiratory rate; 60 cases, 14 per cent, showed a decrease in the respiratory rate, while 65, 15 per cent, showed no change. The average increase in the respiratory rate of those showing a rise was + 9, and the average decrease in those showing a decline was — 4. The total average change in respiratory rate was +6.

NAUSEA AND VOMITING

The incidence of postoperative nausea and vomiting is of interest. In 267 cases, or 62 per cent, nausea and vomiting were entirely absent. In 163 cases, or 38 per cent, there were some nausea and vomiting after operation. For the most part these were very transient and ordinarily could be ascribed to the operation itself rather than to the anesthetic, and in none of the cases were nausea and vomiting greatly prolonged, as one occasionally sees after deep ether narcosis.

REACTION TIME

Of particular interest was the time required for reaction. Table 9 shows in a statistical way the time interval between the conclusion of the operation and the time when reaction took place. It will be noted that in a small group of 10 cases the patients reacted immediately after the operation, while approximately 23 per cent of the patients reacted in less than one hour. The largest group was composed of 204 patients, or 47 per cent of the total number. These patients reacted between one and three hours, whereas the next largest group reacted between three and six hours, and a comparatively small number required more than six hours for reaction. The longest reaction time recorded was eighteen hours, and the second longest period fifteen hours. Further mention of the two patients who died without reacting will be made

TABLE 9.—*Reaction Time*

Time	Number	Per Cent
Immediate....................	10	2.48
2 to 15 min.......	44	10.25
15 min. to 1 hr....	45	10.56
1 to 3 hr..............	204	47.52
3 to 6 hr.........	104	24.22
6 to 12 hr............	16	3.73
Over 12 hr............	5	1.24
	428	100
Died without reacting.....	2	
	430	

Average reaction time—2½ hr.

later. The average reaction time as computed for all of the cases amounted to two and one-half hours. At the present time, I am trying the effect of withdrawal of the residual avertin solution from the rectum at the conclusion of the operation. Following this, a rectal instillation of oil is given. While no definite data are as yet available on the results, there is some evidence to show that the reaction time can be further shortened in this manner. After reacting, the patients were ordinarily drowsy for several hours longer but could be readily awakened for the administration of fluids. In our opinion, there was no increase in the necessity for postoperative catheterizations. A striking and advantageous feature was the subsequent amnesia for this postoperative period.

POSTOPERATIVE COMPLICATIONS

A complete tabulation of all complications arising during convalescence was made. Table 10 lists the major nonfatal complications which were found and also the time of their appearance. Of especial interest in this connection is the group of cases in which postoperative pulmonary complications developed which might be attributed to the

anesthetic. On the assumption that such complications will make their appearance within five days after operation, the cases in which there were pulmonary complications that might be charged to avertin are marked with an asterisk. The first 4 cases in the table fall into this category. They consisted of 2 cases of bronchitis, 1 of pleurisy and 1 of bronchopneumonia. All of the patients recovered under the usual treatment. Case 257443, in which a nephrectomy was done for renal tuberculosis, was that of a patient with other associated tuberculous

TABLE 10.—*Postoperative Complications*

Case No.	Age	Sex	Operation	Anesthetic Combination	Complications	Time of Development After Operation
266266*	29	M	Inguinal herniotomy and orchidopexy	110 mg. per Kg. and gas	Pneumonia	2nd day
265910*	50	M	Spinal fusion	110 mg. per Kg. alone	Pleurisy	2nd day
276750*	43	M	Cholecystectomy and appendectomy	110 mg. per Kg. and gas	Bronchitis	4th day
265890*	29	F	Cholecystectomy and appendectomy	110 mg. per Kg. and ether	Bronchitis	3rd day
250033	40	F	Cholecystectomy and appendectomy	110 mg. per Kg. and gas	Pulmonary infarct or bronchopleurisy at base of right lung	2 wk.
261776	37	F	Cholecystectomy	110 mg. per Kg. and ether	Respiratory paralysis	Immediately
255423	75	M	Colostomy for carcinoma of rectum	110 mg. per Kg. and gas	Heart block (advanced myocarditis)	2nd day
257443*	34	F	Nephrectomy for tuberculosis	115 mg. per Kg. and gas	Bronchopneumonia? tuberculous	2nd day
269856	47	M	Cholecystogastrostomy for carcinoma of pancreas	110 mg. per Kg. alone	Pleurisy with effusion	11th day
278866*	33	M	Drainage of appendical abscess	110 mg. per Kg. and gas	Respiratory paralysis	2nd day
238818	36	M	Abdominal sympathectomy	130 mg. per Kg. alone	Postoperative mania (psychogenic)	For 2 wk.

lesions, and the pneumonia, which developed on the second postoperative day, was thought possibly to be a tuberculous pneumonia. The acute condition cleared up promptly, but the patient was placed on the usual regimen ordinarily prescribed for patients with pulmonary tuberculosis. Case 270866 must be included among the pulmonary complications. This patient, shortly after being returned to the ward following operation, had a temporary respiratory arrest, for no clear reason. Under appropriate treatment he was resuscitated, and the remainder of the convalescence was without event. In case 261776 likewise, temporary paralysis occurred. Here, however, it was thought that this was due to a slip in the ward routine. The patient, who had had a preliminary dose of morphine and hyoscine before the administration of the avertin, was returned to the ward following

operation in good condition but still deeply narcotized. On her return, through a misunderstanding of orders, the nurse in charge at once administered ¼ grain of morphine subcutaneously. Shortly after this there was a cessation of respiration, although the pulse remained practically normal. Artificial respiration was instituted at once, and after a period of about fifteen minutes normal respiration again took place, and there was nothing further to mar the convalescent period. This undoubtedly was due to an error in management, and it was felt that had the additional morphine not been given this complication could have been averted.

In the entire series there was no evidence of rectal irritation or ulceration from the use of avertin in any case. No case was discovered in which there was bleeding or discharge from the rectum, and no symptoms such as rectal pain or discomfort were encountered following the use of avertin. This we attribute to the fact that great care was exercised in the preparation of the solution, as it seems to have been satisfactorily proved that the early cases in which such complications ensued were undoubtedly due to the fact that either decomposed preparations or solutions of improper p_H value were used.

Likewise, there was no evidence that repeated administrations of the drug were attended with additional danger. Several instances occurred in the series in which avertin was used repeatedly without ill effect. One man in the course of a year had nine plastic operations, all done with avertin, and a woman with gallstones, who refused operation, received six full sized doses in a period of two weeks for the control of intolerable pain.

DEATHS

In the 430 cases, there were 22 deaths, or a mortality of 5.1 per cent. It can be readily seen from table 11 that in most instances the deaths were due to causes other than the anesthetic, and for the most part the fatal issue took place a considerable time after the operation was performed. The cases in which the anesthetic may have been or probably was a factor have been marked with an asterisk and might be mentioned individually. Case 272390 undoubtedly must be classified as one of death due to avertin. This patient had a laparotomy for what proved to be an inoperable carcinoma of the stomach with abdominal carcinomatosis. The operation consisted of exploration only. He left the operating room in satisfactory condition but failed to react and died suddenly five hours later. Autopsy showed no positive cause for the sudden death. The most striking observation was a rather intense pulmonary edema.

In case 263327 the patient was a frail little woman with an adenomatous goiter and a damaged myocardium. It will be noted that

the avertin dosage was considerably decreased below the average dose used in the series, and the patient awakened promptly at the conclusion of the operation. However, bronchopneumonia developed, proved by roentgen examination, probably on the basis of postoperative atelectasis, and this proved to be fatal in twenty-four hours.

TABLE 11.—*Number of Deaths*

Case No.	Age and Sex	Operation	Anesthetic Combination	Cause of Death	Time of Death After Operation
259041	48 F	Ventral hernia and fecal fistula	120 mg. per Kg. alone	Generalized sepsis	7 wk.
269951	47 F	Nephrectomy for calculus, pyonephrosis	110 mg. per Kg. alone	Empyema bronchopleural fistula (16th day)	18th day
275073	62 M	Anterior gastro-enterostomy for carcinoma of stomach	120 mg. per Kg. and gas	Renal insufficiency	13th day
254336	25 F	Duodenojejunostomy	110 mg. per Kg. alone	Ulceration at anastomosis site and hemorrhage	8th day
263643	33 M	Multiple compound fracture of mandible and maxilla	130 mg. per Kg. alone	Fat embolism of lung	1 hr.
273841	46 M	Lobectomy of upper and middle lobes for carcinoma of bronchus	110 mg. per Kg. and gas	Pulmonary gangrene	2 days
277839	38 M	Ligation of internal jugular and ablation of sigmoid sinus for sigmoid sinus thrombosis	110 mg. per Kg. and gas	Cavernous sinus thrombosis	13 days
257273	18 M	Reamputation of thigh for septic knee	110 mg. per Kg. and gas	Bronchopneumonia	33 days
255786	34 F	Left nephrolithotomy	110 mg. per Kg. and gas	Pyelonephritis	3 wk.
267018	27 F	Splenectomy for purpura hemorrhagica	110 mg. per Kg. and gas	Continued hemorrhage	3 days
257655	57 M	Polya resection for gastric ulcer	110 mg. per Kg.	Renal insufficiency and urinary suppression	5 days
270669	23 M	Thigh amputation for tuberculosis of the knee	110 mg. per Kg. alone	Widespread tuberculosis	41 days
270308	69 F	Bilroth II for carcinoma of stomach	110 mg. per Kg. alone	Intestinal fistula	15 days
191783	65 M	Sublingual abscess, endothermy	110 mg. per Kg. alone	Septicemia	6 days
272390*	49 M	Exploratory laparotomy for carcinoma of stomach with carcinomatosis	110 mg. per Kg. and gas and ether vapor	Did not react	5 hr.
252395	33 F	Ureterostomy for carcinoma of bladder	110 mg. per Kg. and gas and ether vapor	Metastatic carcinoma and pyelonephritis	22 days
263327*	55 F	Thyroidectomy for adenomatous goiter	80 mg. per Kg. and gas	Atelectasis and bronchopneumonia	24 hr.
278395*	57 M	Gastrostomy for carcinoma of esophagus and tracheo-esophageal fistula	110 mg. per Kg. alone	Extensive carcinoma; did not react	24 hr.
278243	57 M	Polya resection for carcinoma of stomach	110 mg. per Kg. alone	Peritonitis	14 days
216624*	56 M	Metastatic carcinoma of neck glands (primary in tongue); excision of glands with ligation of internal carotid artery	110 mg. per Kg. and gas	Right hemiplegia (2nd day after operation; bronchopneumonia (5th day after operation)	8th day
279539	52 F	Cholecystostomy for carcinoma of gallbladder with stones and empyema of gallbladder	110 mg. per Kg. and ether	Duodenal fistula (carcinoma)	29th day
273282	53 F	Bilateral ureteral transplant and cystectomy for carcinoma of bladder	110 mg. per Kg. alone	Cardiac failure	2nd day

In case 278395, the patient was an extremely emaciated man who had a cancer of the esophagus complicated by a tracheo-esophageal fistula. While his condition was desperate, a gastrostomy seemed to be clearly indicated. This operation is ordinarily performed under local anesthesia, but in this particular case avertin was chosen in order that a satisfactory examination of the trachea with biopsy might be carried out. This patient also failed to react from the avertin narcosis and died twenty-four hours later. An autopsy was not obtained.

In case 216624, the patient was a man with an extensive metastatic carcinoma of the cervical glands for which a radical resection was done. In the course of the operation it became necessary to ligate the internal carotid artery with the unfortunate consequence that a hemiplegia developed on the second postoperative day, and on the fifth day there was definite evidence of bronchopneumonia from which the patient died on the eighth day.

In case 273841, the patient was a man with carcinoma of the right primary bronchus. In doing a lobectomy of the upper and middle lobes, the main pulmonary artery was accidentally tied, which accounted for the gangrene of the lower lobe, which proved to be fatal on the second postoperative day.

Considering these two tables together, there were 8 cases of postoperative pulmonary complications, for the occurrence of which the anesthetic probably played a part. This gives a percentage of postoperative pulmonary complications of 1.9 per cent. Of these postoperative pulmonary complications, there were 4 frank pneumonias, giving a percentage of 0.9 per cent for the entire series. Of the postoperative pneumonias, 2 were fatal, giving a percentage of 0.5 per cent for the entire series, and of 50 per cent for the postoperative pneumonias.

SUMMARY

The results from the use of avertin in this series of selected cases were on the whole highly satisfactory. The easy induction was one of the outstanding features and one that made avertin particularly agreeable to the patients. Avertin proved to be of especial value in operations on the head and face, in which many times it was possible to dispense completely with cumbersome apparatus such as gas masks or ether cones. Perhaps its sphere of greatest value was in abdominal surgery where, when combined with some supplemental anesthetic agent, it aided considerably in enhancing muscular relaxation. We are not prepared to advocate it as having any decided advantages in thyroid surgery. While it is admirably suited to the "steal" type of operation, it has not seemed that the quality of the anesthesia in these cases was importantly better when avertin was employed, and there are objections

both theoretical and actual to a prolonged period of somnolence after operation in this type of case. In such cases it seems particularly desirable to avoid abolition of the cough reflex, when mucus is apt to accumulate in the throat and attendant laryngeal edema is often present.

CONCLUSIONS

1. A representative group of 430 surgical cases in which avertin was employed for anesthesia or basal narcosis has been analyzed.

2. The quality of surgical anesthesia produced by avertin unassisted or supplemented by gas or ether in most cases is entirely satisfactory. The induction from the standpoint of the patient is probably less unpleasant than that attendant on any other form of anesthetic.

3. In this series some form of supplemental anesthetic, such as nitrous oxide and oxygen or ether, was required in approximately 70 per cent of the cases, the operation in the remaining 30 per cent being performed without reinforcement.

4. While there was usually a preliminary fall in both systolic and diastolic blood pressure, this did not seem to be sufficient to cause alarm, and at the conclusion of the operation the pressure had practically reached the preoperative level. Falls in blood pressure were satisfactorily combated with ephedrine or epinephrine.

5. When nitrous oxide and oxygen were employed as a supplemental agent, the percentage of oxygen in the mixture could be increased to practically twice the amount possible when used with nitrous oxide alone. Likewise, if ether was used to supplement the avertin, the total quantity employed during the operation was considerably less than would have been required for straight ether anesthesia.

6. The average reaction time was two and one-half hours. The majority of the patients reacted between one and three hours, while about 23 per cent reacted in less than one hour.

7. Of the 22 operative deaths occurring in the series, only 4 seemed to have any definite relation to the type of anesthesia. In the entire series there were only 8 cases of postoperative pulmonary complications which seemed in any probability attributable to the avertin. Of these 8 cases of postoperative pulmonary complications, 4 were of pneumonia, and of these 4 postoperative pneumonias, 2 were fatal.

8. In order to avoid unnecessary dangers, it seems that considerable care should be exercised in selecting cases. If this is done, avertin, in my opinion, is not only a safe but an important addition to the anesthetic armamentarium.

SPLENECTOMY IN THE TREATMENT OF HEMORRHAGIC PURPURA

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LOS ANGELES

Thrombocytopenic purpura hemorrhagica is characterized clinically by pathologic hemorrhage, ranging from a massive loss in the acute form, usually with a rapid termination, to the milder form, lasting for years. The blood platelets or thrombocytes show marked reduction. Until recently, splenectomy in the fulminating form was considered contraindicated and futile. Killins,[1] Reuben and Claman [2] and others, however, have reported recoveries from the acute form following splenectomy.

The success of splenectomy in the majority of cases of the chronic form is conceded. A certain number of failures are reported, and these are difficult to explain. Giffin and Holloway [3] found no clinical or hematologic improvement in 4 of their 28 cases. Spence,[4] out of 101 cases abstracted, found 15 per cent with a return of symptoms.

The commonly accepted theory for the successful results after splenectomy regards the spleen as abnormally destructive to platelets, producing thrombocytopenia and its sequelae. The whole reticulo-endothelial system is diseased, and the spleen exerts the greatest destructive influence. Better results follow splenectomy performed on persons with the largest spleens and seem to corroborate this idea. Removal of the spleen usually is followed in a few hours by a marked rise in the blood platelets, and rarely is there postoperative bleeding. The great bulk of reticulo-endothelial tissue is represented by the spleen, and its extirpation usually is adequate. Return of symptoms theoretically should suggest increased activity or hyperplasia of the remaining reticulo-endothelial tissue.

1. Killins, W. A.: Acute Thrombocytopenic Purpura Cured by Splenectomy, J. A. M. A. **92**:1832 (June 1) 1929.

2. Reuben, M. D., and Claman, L.: Splenectomy in Acute Thrombocytopenic Purpura Hemorrhagica, Arch. Pediat. **45**:84 (Feb.) 1928.

3. Giffin, H. Z., and Holloway, J. K.: A Review of Twenty-Eight Cases of Purpura Hemorrhagica in Which Splenectomy Was Performed, Am. J. M. Sc. **170**:186 (Aug.) 1925.

4. Spence, A. W.: Results of Splenectomy for Purpura Hemorrhagica, Brit. J. Surg. **15**:466 (Jan.) 1928.

That the return of symptoms is often due to an unnoticed accessory spleen is suggested by Morrison, Lederer and Fradkin.[5] They described a patient whose spleen was removed, but in whom a small accessory spleen was allowed to remain. Improvement was immediate but transient, and in a year the patient was bleeding again. They suggested hypertrophy of the remaining accessory spleen as an explanation. They believe the relative frequency of supernumerary spleens, often situated in aberrant abdominal foci, can account for many unsatisfactory results. They enjoin a careful search for accessory splenic tissue during splenectomy.

On the other hand, many patients show clinical improvement, with relief from hemorrhagic symptoms, and still fail to show satisfactory improvement in the hematologic findings. The platelets may remain low, the bleeding time prolonged, the tourniquet test positive and the blood clot nonretractile and still the patient will show no spontaneous ecchymosis, oozing gums or other hemorrhage from the mucous membranes.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis between purpura hemorrhagica and other blood dyscrasias when typical is comparatively sure, save in some fulminating types. Aplastic anemia, in the bleeding stage, is characterized by extreme anemia, marked leukopenia and reduction of the granulocytes, with no splenomegaly. Acute leukemia, especially if in the aleukemic stage and without peripheral adenopathy, may present difficulties. There may be splenomegaly, but the differential count of the white cells will usually show immature lymphocytes and lymphocytosis. In acute purpura hemorrhagica, the red count at the onset is not usually markedly reduced, anemia occurring in proportion to the loss of blood. The hemophilic person shows marked prolongation of the coagulation time and a normal bleeding time.

ATYPICAL HEMORRHAGIC DISEASE

Recent literature has been instructive in showing the many atypical cases of hemorrhagic disease that occur. Glanzman,[6] Rothman and Nixon,[7] Minot [8] and others described a familial type of purpura hemorrhagica without thrombocytopenia. A normal platelet count is associated

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5. Morrison, M. D.; Lederer, M., and Fradkin, W. Z.: Accessory Spleens, Their Significance in Essential Thrombocytopenic Purpuric Hemorrhagica, Am. J. M. Sc. **176**:672 (Nov.) 1928.

6. Glanzman, E.: Hereditäre hämorrhagische Thrombasthenie, Jahrb. f. Kinderh. **88**:1 and 113, 1918.

7. Rothman, P. E., and Nixon, N. K.: Familial Purpura Hemorrhagica Without Thrombopenia, J. A. M. A. **93**:16 (July 6) 1929.

8. Minot, G. R.: A Familial Hemorrhagic Condition Associated with Prolongation of the Bleeding Time, Am. J. M. Sc. **175**:301 (March) 1928.

peculiarly with a prolonged bleeding time, a nonretractile clot and a positive tourniquet test. The patients have all the clinical phenomena of purpura hemorrhagica. The platelets in this condition are believed to be qualitatively defective; hence the term "thrombasthenic" purpura in distinction to thrombocytopenic purpura.

In addition to one of the familial types, Giffin [9] reported another case, in a patient aged 9, with all the features of hemorrhagic purpura except thrombocytopenia. Bleeding from the mucous membranes occurred, with a prolonged bleeding time and a nonretractile clot but a normal number of platelets. Splenectomy was done, without the usual prompt improvement such as follows typical purpura hemorrhagica.

Sweeney [10] reported an atypical case in which the diagnosis was extremely difficult. Clinically, the patient had marked hemorrhages, but despite a greatly prolonged bleeding time the platelets were not reduced. The white cells were normal. He was given numerous transfusions of blood, but failed to improve, and as a last resort a splenectomy was done. There was a slight transient rise in the white cells, but no increase in the platelets and no improvement clinically. The patient died about six months later.

Kennedy [11] described the case of a child aged 4, with a prolonged bleeding and coagulation time, decreased platelets, intense anemia and slight leukocytosis. A splenectomy was done without improvement. Two months later tonsillectomy was followed by excessive hemorrhages and death. Necropsy revealed an aplastic bone marrow. The patient had an atypical aplastic anemia. Splenectomy in the cases reported by Giffin and Kennedy for familial thrombo-asthenic purpura hemorrhagica has not given the satisfactory results obtained in pure thrombocytopenic purpura. Little and Ayres [12] reported a death following splenectomy in a case of hereditary hemorrhagic purpura with a normal platelet count.

The most careful scrutiny of all patients with hemorrhagic disease is indicated before splenectomy is resorted to. Many cases are not typical, and the differential diagnosis is most difficult. In borderline cases with no improvement, splenectomy is perhaps justifiable if the hemorrhage is unrelieved by transfusion and death seems otherwise inevitable. The cases of acute bleeding, as described by Kennedy [10] and Killins,[1] were of this type. In the chronic type of bleeding with

9. Giffin, H. Z.: Unusual Types of Hemorrhagic Disease, Am. J. M. Sc. **175**:44 (Jan.) 1928.

10. Sweeney, J. S.: Chronic Aplastic Anemia and Symptomatic Purpura Hemorrhagica Probably Due to Benzol Poisoning, Am. J. M. Sc. **175**:317 (March) 1928.

11. Kennedy, R. L. J.: Diseases of Children Benefited by Splenectomy, J. A. M. A. **91**:874 (Sept. 22) 1928.

12. Little, W. D., and Ayres, W. W.: Hemorrhagic Diseases, J. A. M. A **91**:1251 (Oct. 27) 1928.

ecchymoses, bruising and moderate anemia we believe that it is better to postpone splenectomy unless the following requisites are met: (1) splenomegaly; (2) thrombocytopenia; (3) prolongation of the bleeding time; (4) nonretractility of the blood clot; (5) positive tourniquet test showing decreased capillary resistance; (6) normal coagulation time and (7) a normal or slightly increased leukocyte count.

The following case illustrates the clinical recovery following splenectomy in typical chronic hemorrhagic purpura, without, however, a hematologic recovery.

REPORT OF A CASE

Miss M. S., aged 36, reported that at the age of 14 she noticed numerous spots on the legs about the size of a dime or greater, occurring without any bruising or injury. She was nicknamed "Spotty" by her playmates. At the age of 16 she was bitten on the arm by a mosquito, and a black and blue spot about 2 inches (5 cm.) in diameter developed at the site. At 19 she had an acute, severe pain in the lower part of the abdomen and fainted. In college she noticed that the discharge during her menstrual periods became profuse. Occasionally, a severe spontaneous vaginal hemorrhage developed.

In 1920, tonsillectomy was advised in the belief that the purpura was possibly due to infection. She lost a great deal of blood, and it was thought she would not live. Transfusion of blood was not resorted to, and the bleeding finally was stopped by clamps.

In October, 1922, she had another acute attack of abdominal pain associated with vomiting, believed to be acute appendicitis. She was seen by a physician, and for the first time was told that she had purpura hemorrhagica. Splenectomy had not yet been established in America as accepted treatment, and she forsook regular medical care for osteopathy. Brill and Rosenthal's [13] paper, in 1923, brought splenectomy a more generalized recognition, although Kaznelson [14] had reported the first case in 1916.

In 1923, she had a severe uterine hemorrhage.

In the summer of 1928, she had another attack of severe abdominal pain, during which she became very faint and weak. There was no external bleeding, but she became so anemic that she was given her first transfusion of blood. About this time, she first noticed a little oozing of blood from the gums and observed blood spots on her pillow in the morning.

In August, 1929, she was seized with griping abdominal pain, and vaginally passed several clots of blood. She had marked bleeding from the gums, the bleeding continuing for thirty-six hours. The vaginal bleeding finally was stopped by packing. She was seen at the office on Aug. 27, 1929. The skin was markedly pale, the mucous membranes washed out. A number of ecchymoses were present on the arms and legs. The spleen was enlarged two fingerbreadths below the costal margin. Changes in the blood typical of chronic thrombocytopenic hemorrhagic purpura were present and splenectomy was advised. She had another attack

13. Brill, N. E., and Rosenthal, N.: Treatment by Splenectomy of Essential Thrombocytopenia (Purpura Hemorrhagica), Arch. Int. Med. **32**:939 (Dec.) 1923; The Curative Treatment by Splenectomy of Chronic Thrombocytopenic Purpura Hemorrhagica, Am. J. M. Sc. **166**:503 (Oct.) 1923.

14. Kaznelson: Wien. klin. Wchnschr. **29**:1451, 1916.

of severe pain in the lower part of the abdomen and menorrhagia the next month; after its cessation she was admitted to St. Vincent's Hospital on November 1.

She was bleeding from the gums, and numerous suggillations were present on the body. The site of a hypodermic injection became swollen and discolored. The

TABLE 1.—*Changes in the Blood in Our Case of Purpura Hemorrhagica*

	Red Blood Cells In Millions	Hemoglobin, per Cent	Leukocytes in Thousands	Polymorphonuclear Leukocytes, per Cent	Platelets in Thousands	Bleeding Time, Minutes	Clot Retractility	Tourniquet Test
Before splenectomy								
90 days.........	4.4	25	9.7	61	...	..	Negative	Positive
13 days.........	3.0	20	6.4	74	50	20	Negative	
8 days.........	3.1	25	5	..	...	20	....	Positive
8 days..........	Direct transfusion—500 cc. whole blood							
4 days.........	3.5	30	4.6	79	80			
2 days.........	Direct transfusion—500 cc. whole blood							
2 days.........	3.8	34	5	78	150	14		
	Splenectomy followed by transfusion—500 cc. blood							
After splenectomy								
1 day..........	4.4	42	57	94	177			
2 days..... ...	...	..	55	96	160	4.5	Present	Negative
4 days.........	4.2	39	33 ..	87				
6 days.........	4.2	38	25	86	310	..	Present	Negative
9 days.........	4.2	41	16.5	80	380			
15 days.........	4.4	46	17	78	250	4		
20 days.........	4.4	45	14	79	240			
27 days.........	4.4	50	12.7	80	280	4		
6 months......	3.8	..	15	64	190	5		
9 months......	3.9	35	19.1	58	...	3		
11 months......	5.8	59	16	52				
13 months......	4.9	67	18	68				
18 months......	4.7	65	15	58	29	2.5	Absent	Positive

TABLE 2.—*The Main Changes in the Blood in Hemorrhagic Disease*

	Purpura Hemorrhagica		Aplastic Anemia	Acute Leukemia	Hemophilia
	Acute	Chronic			
Splenomegaly..............	Not usually	Present	Not present	Variable	Not present
Anemia....................	Proportionate to bleeding	Proportionate to bleeding	Marked anemia before bleeding	Proportionate to bleeding	Variable, depends on loss of blood
White blood cells...........	Normal or increased	Normal or increased	Marked leukopenia	Leukemic normal or aleukemic	Normal
Differential blood study....	Normal	Normal	Granulocytopenia	Atypical immature lymphocytes	Normal
Bleeding time..............	Increased	Increased	Increased	Increased	Normal
Blood platelets.............	Reduced	Reduced	Reduced	Reduced	Normal count
Coagulation time..........	Normal	Normal	Normal	Normal	Markedly prolonged
Heredity.................. ..	May be familial type	May be familial type	Negative	Negative	Familial

bleeding time was twenty minutes, the platelet count, 50,000. She was given a transfusion of whole blood on November 10 and again on November 12, with only slight improvement in the bleeding time. Splenectomy was done on November 14, followed by an immediate tranfusion, which was given as a precautionary measure, as there was no postoperative bleeding from the wound.

The pathologic report by Dr. E. M. Hall was as follows:

"The spleen is about two and one-half times normal size, and measures 15 by 9 by 5 cm. The capsule is smooth. There is a deep fissure near the upper third. The cut surface has a meaty appearance, the marking is indistinct, and the consistency firm.

"Sections stained with Giemsa show moderate, diffuse fibrosis, marked congestion, marked hypertrophy and hyperplasia of the endothelial cells of the venous sinuses. The venous spaces also contain a few polymorphonuclear leukocytes and an occasional eosinophil and normoblast. The diagnosis is chronic purpura hemorrhagica."

Clinically, there was a complete disappearance of oozing from the gums and purpuric spots the day after splenectomy. The blood changes are shown in the chart and table. About the sixth postoperative day, the patient complained of a rheumatic pain in her left shoulder, and signs of fluid gradually developed in the left pleural cavity. On the fourteenth postoperative day, a temperature of 101 F. developed. The chest was tapped on December 1, and 1,500 cc. of red turbid fluid was removed. This proved to be sterile. Following this the fever dropped, and there was no recurrence. She was discharged in good condition one month after splenectomy.

COMMENT

This case illustrates the rather typical response of the blood picture to splenectomy. A tremendous leukocytosis, due to proliferation of the granular leukocytes, was found the day after splenectomy. This slowly decreased, but a year later the white cell count was still elevated. The frequency with which this is found after splenectomy for purpura hemorrhagica suggests the existence of a leukotoxin in addition to the supposed lysin that destroys the platelets. The persistent leukocytosis is unexplainable. Evans,[15] in reporting the blood changes following splenectomy, found no persistent leukocytosis. The white cells were usually normal within a month.

The slower rise in platelets, reaching the maximum about the eighth day after operation, is characteristic. The response, however, was moderate, the count failing to rise to the frequent level of from 500,000 to 1,000,000.

The immediate return to normal of the bleeding time after splenectomy was coincident with the rise of platelets. Over a period of a year and a half since the operation, there has occurred a gradual reduction of the platelets, but despite this, the clinical improvement has continued. There has been a gain in weight and strength. The patient is again teaching.

The end-result of the splenectomy as seen a year later was a clinical cure, but only moderate hematologic improvement. The so-called essential factor in the production of the disease, thrombocytopenia, had

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15. Evans, W. H.: The Blood Changes After Splenectomy in Splenic Anemia, Purpura Hemorrhagica and Acholuric Jaundice, with Special Reference to Platelets and Coagulation, J. Path. & Bact. **31**:815 (Oct.) 1928.

reappeared, but the usual sequel, pathologic hemorrhage, had not. The blood clot again failed to retract; there was a shower of petechiae on application of the tourniquet, but no oozing of the gums or menorrhagia. Again, atypically and peculiarly, the bleeding time was normal.

That there is an additional factor responsible for the disease other than the thrombocytopenia is indicated by this and other reports. Apparently, clinical hemorrhagic purpura can appear when the platelets are normal in number, as in the "thrombasthenic" type, usually familial. Conversely, a patient may have a marked reduction of the blood platelets without clinical purpura hemorrhagica.

It follows that the sole explanation for the clinical cure of purpura hemorrhagica in the majority of cases by splenectomy cannot be the postoperative elevation of the platelets. It is concomitant with improvement, but the effect of splenectomy is more complex and far-reaching than it has yet been possible to explain.

SUMMARY

The salient facts in the literature concerning so-called chronic essential thrombocytopenic purpura have been reviewed. A number of atypical cases of unusual hemorrhagic disease have been cited, and the futility of treatment for such cases by splenectomy pointed out. The necessity for a meticulous scrutiny of all hemorrhagic patients to eliminate atypical cases such as "thrombasthenic" purpura is suggested.

A case showing a clinical recovery but a hematologic failure is described. Thrombocytopenia apparently is not the only factor operating in purpura hemorrhagica.

PASSAGE OF CHOLESTEROL THROUGH THE MUCOSA OF THE GALLBLADDER

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For the past number of years the question of the etiology of cholesterosis of the gallbladder has assumed widespread interest.

In a series of 5,000 gallbladders removed at operation, MacCarty,[1] in 1919, found cholesterosis of the gallbladder to be present in 18 per cent of his cases. In 1921, Mayo[2] found cholesterosis in 39 per cent of 1,254 cases of disease of the gallbladder. Mentzer[3] in 1926 published autopsy reports of .612 cases, with an incidence of cholesterosis as high as 38 per cent. In 1929, Illingworth[4] noted cholesterosis in 21 of 100 consecutive gallbladders removed at operation.

Anywhere from 20 to 50 per cent of these cases of cholesterosis were associated with gallstones, usually composed of pure cholesterol.

Cholesterosis, so named by Mentzer[5] in 1925, is a pathologic condition of the mucosa of the gallbladder, consisting macroscopically of tiny yellowish granules lying beneath the epithelium. Microscopically, in a Sudan-stained section, lipoid material may be seen deposited at the bases of the epithelial cells and in the large mononuclear endothelial cells of the stroma. In the majority of cases the subepithelial coat appears thickened by a varying amount of fibrous connective tissue. Very often scattered areas of small round cells may be seen. As a result of the combined fibrosis and the excessive deposits of lipoid material, the so-called "villi" of the mucosa are, as a rule, found to be shortened and thickened, but occasionally may be elongated and bulbous, or even definitely papillomatous in appearance.

1. MacCarty, W. C.: Ann. Surg. **69**:131, 1919.
2. Mayo, C. H.: Minnesota Med. **4**:1, 1921.
3. Mentzer, S. H.: Surg., Gynec. & Obst. **42**:782, 1926.
4. Illingworth, C. F. W.: Brit. J. Surg. **17**:203, 1929.
5. Mentzer, S. H.: Am. J. Path. **1**:383, 1925.

Virchow first noticed what he considered to be cholesterol in the mucosa of the gallbladder in 1857. Moynihan in 1909 described the macroscopic condition aptly named by MacCarty the "strawberry" gallbladder. It remained for Boyd,[6] however, in 1922, to show that the yellow material found in the wall of the gallbladder in these conditions was undoubtedly cholesterol. He demonstrated that the normal dried mucosa of the gallbladder contained about from 0.5 to 1 per cent of cholesterol, whereas the dried mucosa of the strawberry gallbladder could contain as much as 60 per cent of the substance.

Although various authors have differed in their opinions as to whether inflammation plays any part in the production of cholesterosis, Illingworth [4] has shown experimentally that by feeding rabbits a high cholesterol diet and at the same time producing a chronic cholecystitis, it is possible to obtain a lesion that corresponds closely to that of cholesterosis in the human being.

Mentzer believes cholesterosis to be essentially a metabolic disturbance. Blaisdell and Chandler [7] were able to produce what they believed to be a cholesterosis of the gallbladder by merely administering a high cholesterol diet to animals.

Since 1906, Aschoff [8] has insisted that cholesterol is absorbed by the mucosa of the gallbladder, having proved experimentally that neutral fats and fatty acids could be easily absorbed. However, he was never able to show any direct proof of the absorption of cholesterol. Torinoumi,[9] by reinjecting a measured quantity of bile into gallbladders in which the cystic ducts had previously been ligated and analyzing this bile from seven to thirty-eight days afterward, produced results that tended to confirm Aschoff's belief of the absorption of cholesterol.

Boyd also believes that cholesterol is absorbed by the mucosa of the gallbladder.

Illingworth [4] injected suspensions containing 3,442 mg. of cholesterol per hundred cubic centimeters of bile into the gallbladder of cats, after tying the cystic duct, and showed that under these conditions a part of the cholesterol was absorbed from the gallbladder. It must be remembered, however, that this concentration of cholesterol is about ten times as great as that which normally occurs in the bile in the gallbladder, and that the medium used was an artificial one.

Naunyn,[10] on the other hand, always considered that the cholesterol of the bile was derived from the mucosa of the biliary passages and

6. Boyd, W.: Brit. J. Surg. **10**:337, 1922.

7. Blaisdell, F. E., and Chandler, L. R.: Am. J. M. Sc. **174**:492, 1927.

8. Aschoff: München. med. Wchnschr. **37**:1847, 1906.

9. Torinoumi: Beitr. z. path. Anat. u. z. allg. Path. **72**:456, 1924.

10. Naunyn, B.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:2, 1921.

gallbladder. His opinion, however, was not based on any direct experimental evidence.

The recent experimental work of Elman and Graham [11] seems to favor the latter view, since their evidence indicates that cholesterol is secreted into the bile in the gallbladder.

It may therefore be seen that two main theories exist as to the origin of cholesterol deposited in the wall of the gallbladder in so-called cholesterosis, and in order to understand the condition in which cholesterol plays so important a part, it is necessary at the outset to determine the function of the normal gallbladder in regard to cholesterol.

Most of the workers in the past have experimented with cholesterol in an artificial suspension and in abnormal concentrations. It has been the aim throughout the present work to use as much as possible the normal concentration of cholesterol as found in animal bile.

The purpose of the following experiments is to determine whether cholesterol passes through the wall of the gallbladder from the bile into the blood stream or lymphatics, or, vice versa, from the blood stream into the bile.

TECHNIC

The technic of the experiments was as follows:

A fistula of the common duct was produced in a dog after the method of McMaster.[12] A cholecystectomy was performed; the common duct was cut across, and a cannula was placed in the proximal end. A soft rubber tube was attached to the cannula and led down to a U-shaped tube in the animal's pelvis, whence a second firmer tube was carried through the abdominal wall to a sterile rubber balloon. The object of the U-shaped tube was merely to prevent any tension on the cannula in the common duct. In this way sterile bile from the common duct could be collected when necessary.

In this series of experiments all animals were treated in the same fashion. The operative procedure was carried out as follows:

Under ether anesthesia the dog's abdomen was opened. The cystic duct was carefully isolated and ligated, special care being taken not to include the cystic blood vessels or lymphatics, especially the main trunks of the latter, which course down in the fatty tissue on the inferior aspect of the duct.

The bile was then aspirated through the fundus of the gallbladder by a no. 14 blunt cannula inserted by means of a trocar, which was withdrawn as soon as the gallbladder was pierced. The gallbladder was emptied as completely as possible. Saline was not used to wash out the lumen, as the experience of some experi-

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11. Elman, Robert, and Graham, E. A.: The Pathogenesis of the "Strawberry" Gallbladder: (Cholesterosis of the Gallbladder), Arch. Surg. 24:14 (Jan.) 1932.

12. McMaster: Studies from Rockefeller Institute for Medical Research, 1924, no. 51, p. 107.

menters has shown that such procedure rapidly tends to injure the delicate mucosa. On the other hand, it was found that by ordinary aspiration practically all the bile could be removed and that only a small amount clinging to the mucosa remained.

The amount of bile aspirated was measured and replaced by an equal quantity of bile derived from a fistula of the common duct of another dog, as described. The opening in the fundus was closed by a fine purse-string suture in such a way as to evert the mucosa. A sample of the bile from the common duct was set aside in each case for a quantitative estimation of cholesterol. It was therefore possible to know the exact quantity of cholesterol that was injected into the lumen of the animal's gallbladder. For convenience, this dilute bile from the common duct is termed "A bile."

At the end of twenty-four hours, the animal was killed and the liver, gall-bladder and common duct were removed intact. This was done in order to be certain that the cystic blood vessels were not included in the ligature around the cystic duct, and that no accessory bile ducts were communicating with the gall-bladder. If either of these errors was found, the experiment was discarded.

If the blood vessels were found intact and the gallbladder was completely isolated, the biliary contents were carefully removed into a small beaker. This was done in such a fashion as not to scrape the mucosa, so that a small portion of the thick inspissated bile was invariably left adherent to the mucosa.

The bile was constantly found to be dark, inspissated and partly precipitated at the end of twenty-four hours. Approximate measurements showed it to be concentrated from two to three times its original volume. This thick viscid bile removed at the end of twenty-four hours is termed the "B bile."

By estimating the total quantity of cholesterol in the A bile and comparing it with the total quantity in the B bile, values are obtained which throw definite light on the cholesterol function of the normal gallbladder during the process of concentration of hepatic bile.

Analysis of the bile cholesterol by the colorimetric method described in the literature was found to be difficult owing to the yellow discoloration present in the extracts. Eventually the method employed was as follows:

A measured quantity of bile was placed into a 100 cc. beaker, and 10 cc. of 20 per cent potassium hydroxide was added. The contents were heated in a water bath for thirty minutes, and 10 cc. of a 30 per cent calcium chloride solution was then slowly added, with constant stirring. Plaster of paris was then added and thoroughly mixed with the contents, which were then dried at 55 C. Extraction was carried out for ten hours in a Soxhlet apparatus, anhydrous ether being used. The ether containing the cholesterol was then poured into a small beaker and the flask rinsed three times with small quantities of fresh ether. After the ether had evaporated at room temperature, the dry residue was extracted with hot chloro-form and an appropriate portion of this compared colorimetrically by the Burchard-Lieberman reaction against a standard solution of cholesterol. By the addition of known amounts of cholesterol to the bile, the loss by this method was never more than 6 per cent.

However, as colorimetric estimations of cholesterol are regarded with some doubt by certain investigators, in dogs V, VII and VIII, the estimations of both A and B biles were carried out by the digitonin method exactly as described by

Gardner.[13] Portions of the A biles in these three cases were also determined by the colorimetric method, with the following results:

	Colorimetric	Digitonin
V A	10.86 mg.	8.85 mg.
VII A	15.47 mg.	14.17 mg.
VIII A	6.58 mg.	6.45 mg.

This correlation between the two methods indicates that the colorimetric method used is sufficiently reliable for our purpose. Most investigators have found the colorimetric method to yield slightly higher results than the digitonin method.

EXPERIMENTAL DATA

The results of the experiments are as follows:

Dog I.—After the cystic duct had been ligated, 10 cc. of hepatic bile derived from the biliary fistula of another dog was injected into the gallbladder. Ten cubic centimeters of this bile was found to contain 3.58 mg. of cholesterol. At the end of twenty-four hours, the animal was killed and the gallbladder removed. Only 2 or 3 cc. of thick, dark viscid bile (B bile) was found inside the gallbladder; on analysis, this material was found to contain a total of 5.46 mg. of cholesterol. This represents in twenty-four hours an increase of 1.88 mg., or 52 per cent, of cholesterol in the contents of the gallbladder. Two facts must be noted: in the first place, only 10 cc. of bile was introduced, and secondly, the A bile had a fairly high cholesterol concentration, 35.85 mg. per hundred cubic centimeters of bile.

Dog II.—In a similar way, this animal had 31 cc. of hepatic bile (A bile) containing 7.05 mg. of cholesterol introduced into the gallbladder. At the end of twenty-four hours, estimation of the contents of the gallbladder showed a total of 28.69 mg. of cholesterol, an increase of 21.64 mg., or 307 per cent. In this case three times as much A bile was used as in the previous animal, and in addition the concentration of cholesterol in the A bile was much less, being only 22.75 mg. per hundred cubic centimeters of bile.

Dog III.—Twenty-nine cubic centimeters of hepatic bile, containing 5.69 mg. of cholesterol, was injected into the gallbladder. At the end of twenty-four hours, 14.76 mg. of cholesterol was recovered from the concentrated contents, an increase of 9.07 mg., or 159 per cent.

Dog IV.—Twenty-five cubic centimeters of hepatic bile containing 3.35 mg. was injected into the gallbladder, and at the end of twenty-four hours 16.23 mg. was recovered, an increase of 12.88 mg., or 384 per cent. It may be interesting to note that the concentration of the A bile was quite low, being only 13.42 mg. per hundred cubic centimeters of bile.

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13. Gardner, J. A., and Gainsborough, H.: Biochem. J. **21**:130, 1927.

Dog V.—Fifty cubic centimeters of hepatic bile containing 8.85 mg. of cholesterol (as estimated by the digitonin method) was injected into the gallbladder, and at the end of twenty-four hours the thick viscid bile, only about one fourth of its original quantity, was found to contain a total of 29.14 mg. of cholesterol by weight (digitonin). The increase was 20.29 mg., or 229 per cent.

Dog VI.—Twenty-five cubic centimeters of hepatic bile, containing 5.01 mg. of cholesterol, was injected. This bile was allowed to remain in the gallbladder for thirty-eight hours. At the end of this period, extremely thick precipitated bile was found to contain a total of 31.26 mg. of cholesterol, an increase of 26.25 mg., or 524 per cent.

Dog VII.—This animal was treated in a manner similar to the preceding ones with the exception that, for ten days previous to injection, 2 Gm. of cholesterol was added daily to the food in order to raise the cholesterol content of the blood. It has been shown that this content can be easily raised in rabbits by a high cholesterol diet.[4] There is some doubt, however, whether hypercholesterolemia can be produced in omnivorous animals. Lemoine and Gerard[14] and Rothschild and Rosenthal[15] have produced evidence that such hypercholesterolemia can occur. We have found it to be so in the case of dogs. Thus, on feeding two dogs, each weighing about 15 Kg., 1 Gm. of cholesterol daily in their food, the cholesterol content of the blood was approximately doubled in one week; in one case it rose from 77 to 155 mg. per hundred cubic centimeters of bile and in the other case from 99 to 208 mg. At the time of operation, 24 cc. of hepatic bile (derived from another dog with a biliary fistula), containing 6.45 mg. of cholesterol, was introduced into the emptied gallbladder. At the end of twenty-four hours, 35.85 mg. of cholesterol was recovered from the contents of the gallbladder, an increase of 29.4 mg., or 455 per cent. From this it would seem that raising the concentration of the cholesterol in the blood increased the amount of cholesterol entering the gallbladder.

Dog VIII.—In this animal, instead of the cholesterol of the blood being raised, the cholesterol of the hepatic bile was raised by adding an excess of sterilized cholesterol to a flask containing sterile hepatic bile and shaking this every few hours for two days. Prior to the operation, the bile was carefully decanted and filtered through several layers of sterile gauze to prevent any particles of cholesterol from being present in the solution. This procedure raised the A bile cholesterol to 47.24 mg. per hundred cubic centimeters of bile. Thirty cubic centimeters

14. Lemoine and Gerard: Bull. et mém. Soc. méd. de hôp. de Paris **33**:931, 1912.

15. Rothschild, M. A., and Rosenthal, N.: Am. J. M. Sc. **152**:394, 1916.

of this bile, containing 14.17 mg. of cholesterol, was introduced into the gallbladder. At the end of tweny-four hours, 27.85 mg. of cholesterol was recovered, an increase of 12.68 mg., or 89.5 per cent. This result indicates that raising the cholesterol of the bile without raising that of the blood decreases the amount of cholesterol passing into the bile of the gallbladder.

The majority of animals used for these experimental purposes are not listed, owing to the fact that at the end of twenty-four hours the wall of the gallbladder in some instances was found to be inflamed or gangrenous in histologic sections; in others, the results were discarded owing to interference with the blood supply or to the presence of aberrant hepatic ducts emptying into the gallbladder above the ligature, occluding the cystic duct. Only the few animals in which no inflammatory changes were seen in the histologic sections of the gallbladder wall are listed in this article.

TABLE 1.—*Results in Experiments on Eight Dogs*

Dog	Dura-tion, Hours	Amount, Cc.		Mg. per 100 Cc. of Bile		Amount, Mg.		Change, Mg.	Percentage Change
		A	B*	A	B*	A	B		
I	24	10	3	35.85	182	3.58	5.46	1.88	52.0
II	24	31	12	22.75	239	7.05	28.69	21.64	307.0
III	24	29	14	19.61	105	5.69	14.76	9.07	159.0
IV	24	25	11	13.42	147	3.35	16.23	12.88	384.0
V	24	50	15	17.7	194	8.85	29.14	20.29	229.0
VI	38	25	10	20.05	312	5.01	31.26	26.25	524.0
VII	24	24	10	26.85	358	6.45	35.85	29.40	455.0
VIII	22	30	15	47.24	185	14.17	27.85	12.68	89.5

* Approximate.

Table 1 gives the main points in the foregoing experiments.

From table 1 it would appear that cholesterol passes into the bile of the gallbladder from without. It will also be noticed that the cholesterol concentration of B bile is only approximate, as it is difficult to measure the B bile accurately after concentration and precipitation has taken place. Nevertheless, it is interesting to note that the milligrams of cholesterol per hundred cubic centimeters in the B bile approximately corresponds to the average blood cholesterol content of the dog. The following four experiments bring this point out more clearly, as in these animals accurate readings of the cholesterol content of the blood were taken during the twenty-four hours that the experiment was taking place. It has been found that the cholesterol content of the blood of these dogs may vary greatly within short intervals, so it was necessary to check the blood at the beginning and the end of the period of concentration of the A bile.

In dogs IX and X no effort was made to raise the cholesterol content of the blood, but cholesterol was added to the bile.

It was found that the solubility of cholesterol in bile depends on the percentage of bile salts present; thus, by adding increasing percentages of sodium taurocholate and excess cholesterol to different portions of a sample of bile, the amount of cholesterol dissolved was raised proportionately to the percentage of bile salts:

	Cholesterol per 100 Cc. Bile
Bile + excess cholesterol	23.0 mg.
Bile + 1% sodium taurocholate + cholesterol	37.4 mg.
Bile + 2% sodium taurocholate + cholesterol	60.6 mg.
Bile + 10% sodium taurocholate + cholesterol	363.0 mg.

Dog IX.—Our procedure was to add sterile sodium taurocholate and cholesterol to sterile hepatic bile, until a high concentration of cholesterol dissolved in the bile was reached; the excess cholesterol was removed by filtration, and the concentration of cholesterol was found to be 184.9 mg. per hundred cubic centimeters of bile. The cystic duct was occluded as before, and 25 cc. of this A bile, containing 36.98 mg. of cholesterol, was introduced into the emptied gallbladder. At the end of twenty-four hours the animal was killed, and approximately 8 cc. of concentrated bile containing 12.5 mg. of cholesterol was removed from the gallbladder, indicating a loss of 24.48 mg. of cholesterol during the period of twenty-four hours. In other words, 8 cc. of B bile contained 12.5 mg. of cholesterol, corresponding to a concentration of approximately 156 mg. of cholesterol per hundred cubic centimeters of bile. The cholesterol of the blood throughout this experiment averaged 170.5 mg. per hundred cubic centimeters of blood, indicating that the loss of cholesterol from the gallbladder resulted in a final concentration of the cholesterol of the bile corresponding to that of the blood stream.

Dog X.—As in dog IX, A bile with an artificially high concentration was used. Twenty-five cubic centimeters containing 34.37 mg of cholesterol (or 137.5 mg per hundred cubic centimeters of bile) was injected. At the end of twenty-four hours, approximately 8 cc. of bile was recovered, which contained only 14.6 mg. of cholesterol (an approximate concentration of 182.5 mg. per hundred cubic centimeters of bile). The average cholesterol content of the blood throughout the experiment was 163.5 mg. per hundred cubic centimeters of blood. In this case there was a loss of 19.77 mg. of cholesterol from the gallbladder, resulting in a final cholesterol concentration of the bile approximately equal to that of the blood.

Dog XI.—This animal was fed 2 Gm. of cholesterol daily, which was mixed with its food. On the sixth day, at the time of operation, the cholesterol content of the blood was 366 mg. per hundred cubic centimeters of blood. At the end of twenty-four hours. it was 296 mg., giving an average cholesterol content of the blood during the period of bile concentration of 330 mg. After the cystic duct was ligated and

the gallbladder emptied, 25 cc. of hepatic bile derived from a biliary fistula of another dog, containing 8.32 mg. of cholesterol (or 33.3 mg. per hundred cubic centimeters of bile), was introduced into the gallbladder. After twenty-four hours, approximately 8 cc. of bile remained, which on analysis contained 25 mg. of cholesterol (or 312.5 mg. per hundred cubic centimeters of bile). The increase by weight of cholesterol at the end of twenty-four hours was 16.68 mg. The final concentration of cholesterol in the bile was approximately 312.5 mg. per hundred cubic centimeters, whereas the average concentration of cholesterol in the blood stream throughout the experimental period was 330 mg. per hundred cubic centimeters of blood. These figures suggest a close relationship between the two.

Dog XII.—The cholesterol content of the blood of this dog was raised to an average of 425 mg. by the measures that were employed in dog XI. Fourteen cubic centimeters of hepatic bile, containing 3.78 mg. of cholesterol (or 27 mg. per hundred cubic centimeters of bile),

TABLE 2.—*Results of Experiments on Dogs IX, X, XI and XII*

Dog	Duration, Hours	Amount, Cc.		Mg. per 100 Cc. of Bile		Amount, Mg.		Change, Mg.	Percentage Change	Blood Cholesterol, Mg. % Average
		A	B*	A	B*	A	B			
IX	24	25	8	184.9	156.0	36.98	12.5	−24.48	− 66.0	170.5
X	24	25	8	137.5	192.5	34.37	14.6	−19.77	− 57.5	163.5
XI	24	25	8	33.3	312.5	8.32	25.0	+16.68	+200.0	330.0
XII	24	14	8	27.0	430.0	3.78	12.9	+ 9.12	+241.0	425.0

* Approximate.

was introduced into the previously emptied gallbladder with the cystic duct occluded. At the end of twenty-four hours, approximately 3 cc. of bile was recovered, which contained 12.9 mg. of cholesterol (or 430 mg. per hundred cubic centimeters of bile). This shows an increase by weight in twenty-four hours of 9.12 mg. The cholesterol concentration of the bile was raised from 27 mg. to approximately 430 mg. per hundred cubic centimeters of bile, corresponding closely to the average cholesterol content of the blood of 425 mg. per hundred cubic centimeters of blood.

The results of the last four experiments are shown in table 2.

COMMENT

From the foregoing experiments it would appear that in normal dogs cholesterol passes into the bile of the gallbladder from without; that is, the cholesterol is derived in some way from the wall of the gallbladder and deposited in the bile. It would also seem logical to assume that the cholesterol is brought to the gallbladder by the blood stream.

It should be remembered that in this work the technic that was employed corresponds closely to the normal physiologic process. Normally, the gallbladder receives dilute hepatic bile. While in contact with the mucosa of the gallbladder, this bile is rapidly concentrated, principally by the removal of water. Changes in the other constituents of the bile that take place within the gallbladder most likely occur concomitantly with the absorption of the water.

The experimental method imitates closely the physiologic process so far as normal hepatic bile is placed in contact with the mucosa of the gallbladder, and concentration of this bile is allowed to proceed for twenty-four hours. In other words, under controlled quantitative conditions the normal process is reproduced, aside from the fact that the gallbladder is not continually receiving hepatic bile owing to the artificial occlusion of the cystic duct.

Before proceeding further, it should be mentioned that two minor inaccuracies are present in this work. First, when the bile is withdrawn from the gallbladder in the initial procedure, a small quantity of this bile is undoubtedly left in the gallbladder, which is not included in the determination of A bile. Second, when the gallbladder is removed to recover the B bile, a certain amount is also left adherent to the mucosa, which, of course, does not enter into the determination of cholesterol. The latter error is unavoidable, as any washing or scraping of the mucosa would be apt to remove some of the delicate membrane, and the cholesterol content of the cells would then be included in the calculations. It is, however, self-evident that these are but slight errors, and in any case the one tends to offset the other.

A careful analysis of the figures in table 1, aside from indicating that cholesterol normally passes from the blood stream into the bile through the wall of the gallbladder, brought up a further interesting observation. The question arose as to whether cholesterol enters the bile of the gallbladder by active secretion or merely by ordinary filtration. If cholesterol enters the gallbladder by filtration, this process should be dependent on the ratio between the cholesterol content of the blood and the bile, and it may be seen from the figures already given that the amount of cholesterol entering the gallbladder apparently does depend (to at least a great extent) on this ratio. In dog VII, which was fed a high cholesterol diet to produce hypercholesteremia, a large increase of cholesterol is found in the bile at the end of twenty-four hours. If, on the other hand, the cholesterol content of the bile is high and that of the blood normal, there is a much smaller interchange of cholesterol at the end of a given time. This fact is well demonstrated in dog VIII, in which cholesterol was artificially added to the A bile, resulting in a very small increase at the end of twenty-four hours.

Further, as Illingworth[4] and Boyd have shown, if very high concentrations of cholesterol are introduced into the gallbladder (that is, higher than the blood) it tends to disappear from the bile of the gallbladder.

Thus in dogs II, III, IV and V, with an average A bile of 18.37 mg. per hundred cubic centimeters of bile, the average increase of cholesterol was 269 per cent at the end of twenty-four hours. In dog VII, which was fed a high cholesterol diet, the increase was 455 per cent. In dog VIII, on the contrary, in which the cholesterol of the blood was probably normal and in which the cholesterol of the hepatic bile was artificially raised, the actual increase in twenty-four hours was only 89.5 per cent. It therefore seemed logical to assume the possibility that if the cholesterol concentration of the bile should be higher than that of the blood, cholesterol would pass from the bile into the blood stream.

With these facts in view, it was decided to perform a series of experiments in which the cholesterol content of the blood was carefully estimated along with that of the bile. As may be seen by table 2, observations were made on two animals (dogs IX and X) in which the cholesterol content of the bile was artificially raised, with that of the blood remaining within normal limits; on two other animals (dogs XI and XII), the cholesterol content of the bile was more or less normal, but that of the blood was definitely raised by feeding a high cholesterol diet. In studying table 2, it is interesting to note that the B bile, irrespective of the concentration of the A bile, tends to approach an equilibrium with the cholesterol content of the blood. Two factors are involved in the production of this apparent equilibrium: (1) the reduction in volume of the A bile by the absorption of fluid; (2) the interchange of cholesterol between the bile and the blood stream, one way or another.

Dog XII, in which there was marked concentration, is a good example of both these points, the bile being concentrated from 14 to 3 cc. in twenty-four hours by the absorption of fluid. The 14 cc. of bile injected contained 3.78 mg. of cholesterol. If this amount of cholesterol remained constant and reduction in volume by removal of water were the only factor, the final 3 cc. of bile would have a cholesterol concentration of 127 mg. per hundred cubic centimeters of bile. Actually the final cholesterol concentration of the B bile was 430 mg. per hundred cubic centimeters of bile, which corresponds closely to that of the blood (425 mg. per hundred cubic centimeters of blood). We may therefore assume that this result was attained by the passage of cholesterol from the blood stream into the bile. In other words, although the absolute increase by weight of cholesterol in twenty-four hours was small (9.12 mg.), the combined effect of reduction in volume and of addition of cholesterol was to raise the cholesterol concentration of the B bile to a level with that of the blood.

In dogs IX and X, the equilibrium of cholesterol concentration between the blood and the bile was attained by the loss of cholesterol from the bile, compensating for the increased concentration due to the loss of fluid. Thus in dog IX the A bile concentration was 184.9 mg. per hundred cubic centimeters of bile (25 cc. containing 36.98 mg.), slightly higher than that of the blood (170.5 mg. per hundred cubic centimeters of blood). As before, if concentration were the only factor involved, the final 8 cc. of bile would show a concentration of 462.25 mg. of cholesterol per hundred cubic centimeters of bile. Actually, the final cholesterol concentration was only 156 mg. per hundred cubic centimeters of bile, approximating that of the blood. This result could be attained only by a loss of cholesterol from the bile of the gallbladder.

CONCLUSIONS

1. In normal animals, with the cystic duct tied, when the cholesterol concentration of the bile is lower than that of the blood, cholesterol passes from the blood through the mucosa of the gallbladder into the bile.

2. When the cholesterol concentration of the bile is higher than that of the blood, cholesterol passes from the bile through the mucosa of the gallbladder into the blood stream.

3. The amount of cholesterol passing through the mucosa and the direction of its passage apparently depend on the blood-bile cholesterol ratio.

EFFECTS ON COMPOSITION OF BLOOD OF PHYSIO-LOGIC SOLUTION OF SODIUM CHLORIDE

WHEN INTRODUCED BY INTRAPERITONEAL INJECTION AND BY STOMACH TUBE IN THE PRESENCE OF LOW BLOOD PRESSURE

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This paper is a continuation of previously reported studies [1] of the effects of the administration of fluids to animals with low blood pressure. In the previous studies, fluid was administered intravenously and subcutaneously. The changes observed in the protein content of the blood were considered important. The present studies were carried out in order to determine the effects of physiologic solution of sodium chloride when introduced by intraperitoneal injection and by stomach tube into animals with low blood pressure. The subcutaneous injection of histamine and graded bleeding were the methods used to produce low blood pressure.

METHODS

All of the experiments were carried out on dogs that were anesthetized with morphine. They gave no evidence of pain during the experiments. Shortly following the administration of the anesthetic, the blood volume was determined by

the dye method,[2] and samples of blood were withdrawn for the control determinations. Physiologic solution of sodium chloride was then introduced intraperitoneally or by stomach tube. When introduced into the peritoneal cavity, it was injected through a needle at a constant rate of 10 cc. per kilogram of body weight per hour for four hours. Samples of blood were removed for the analyses one, two and one-half and four hours following the beginning of the injection of fluid, and one and one-half and three hours following its completion. When given by stomach tube, one half of the amount, equal to 10 cc. per kilogram of body weight per hour for four hours, was given at the beginning of the experiment, and the remainder at the end of two hours. At the completion of the experiment, the amount of fluid remaining in the stomach or peritoneal cavity was measured. Following the withdrawal of a sample of blood, it was replaced by an equal amount obtained from another dog.

Experiments were first performed in which the effects of administration of fluids to normal dogs by the methods described were determined. In subsequent experiments the blood pressure was caused to decline by the withdrawal of blood from the femoral vein at intervals at the rate of 10 cc. per kilogram of body weight per hour for four hours. In the experiments in which the decline in pressure was produced by histamine, a solution of 0.1 per cent histamine phosphate was injected in sufficient amounts to maintain a depression of the blood pressure.

The hemoglobin was determined by the method described by Cohen and Smith.[3] Van Allen tubes were used for the hematocrit readings. The blood for protein analyses was allowed to clot, and the determinations were carried out on blood serum. The proteins were partitioned by the use of 22.2 per cent sodium sulphate, as recommended by Howe,[4] and the total protein content, the albumin content and the globulin content of each sample were determined by the Macro-Kjeldahl method, according to Gunning's modification.[5] On the basis of the original blood volume determined directly by the dye method, changes in blood volume were calculated from alterations in the hemoglobin. From the hematocrit estimations, the relative volumes of red blood cells and of plasma could be calculated. The absolute amount of protein in the circulation was calculated from protein per unit volume and plasma volume.

RESULTS

I. *Effects on the Composition of the Blood of Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity.* —*A.* When the Blood Pressure Remained at a Normal Level: Three experiments were carried out, the results of which were entirely similar. There was a definite increase in plasma volume in each experiment, and a slight decrease in the amount of protein per unit volume. There was a small increase in the calculated absolute amount of protein in the entire

2. Rowntree, L. G., and Brown, G. E.: The Volume of the Blood and Plasma in Health and Disease, Mayo Clinic Monographs, Philadelphia, W. B. Saunders Company, 1929.

3. Cohen, B., and Smith, A. H.: The Colorimetric Determination of Hemoglobin, J. Biol. Chem. **39**:489, 1919.

4. Howe, P. E.: The Determination of the Proteins in Blood, J. Biol. Chem. **49**:109, 1921.

5. Gunning, J. W.: Ueber eine Modification der Kjeldahl-Methode, Ztschr. f. anal. Chem. **28**:188, 1889.

circulation. The changes in albumin and globulin were parallel to those in the total protein. In the three experiments, the average amount of fluid absorbed from the peritoneal cavity was 34 per cent of that injected. The results of these experiments are shown in table 1.

B. When the Blood Pressure Is Lowered by the Subcutaneous Administration of Histamine: The results of these experiments, of which there were three, differ considerably from those of the controls. There was a diminution in the amount of blood plasma in the circulation in all experiments. The percentage of protein per unit volume of plasma changed little. There was definite diminution in the absolute amount of plasma protein. The results of these experiments are given in table 2.

C. When the Blood Pressure Is Lowered by Hemorrhage: Two experiments were performed. The results obtained were essentially the same in each. The diminution of plasma volume was less than the amount present in the blood that was removed. There was a slight decrease in the percentage of protein. The absolute amount of protein in the circulation decreased, but if correction is made for the amount of protein removed in the blood a slight gain was shown. These figures are placed in brackets in the tables. An average of 24 per cent of the fluid placed in the peritoneal cavity during the two experiments was absorbed. The results of these experiments are shown in table 3.

II. *Effects on the Composition of the Blood of Introduction of Physiologic Solution of Sodium Chloride into the Stomach.—A.* When the Blood Pressure Remains at a Normal Level: The administration of physiologic solution of sodium chloride by stomach tube to dogs the blood pressure of which remained at essentially the normal level throughout the experiment caused little alteration in the percentage of protein of the blood serum. The results of one of the three experiments showed considerable loss of plasma during the experiment and a comparable loss of total protein. There was a slight increase in plasma volume in one experiment and a very slight diminution in the other. In the former, the absolute amount of protein in the circulation at the end of the experiment was almost exactly the same as at the control period, while in the latter, 2 Gm. of protein was lost during the seven hours. The results of these experiments are shown in table 4.

B. When the Blood Pressure Is Caused to Decline by the Subcutaneous Administration of Histamine: In both experiments of this series there was definite and considerable diminution in the plasma volume and comparable loss of protein. The protein per unit volume remained constant, and these results are essentially identical with those obtained when histamine is injected and no fluid is administered. Almost as much fluid

TABLE 1.—*Effects on the Composition of the Blood of the Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity*

Experiment	Time from Beginning	Amount of Fluid Given	Total Protein		Albumin		Globulin		Blood Volume from Hemoglobin and Hematocrit			Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
			Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Red Blood Cells	Plasma	Whole			
T 154 16.9 Kg.	Control	0	7.2	65.4	3.00	27.8	4.20	37.6	(637)	(928)	(1,565)	40.7	87.7	122
	1 hr.	163	7.2	67.2	3.08	29.4	4.12	37.8	637	955	1,592	40.0	86.2	105
	2 hr. 30 min.	386	7.2	66.3	3.00	28.5	4.20	38.3	646	949	1,595	40.5	86.0	122
	4 hr.	672	6.64	62.6	2.94	27.7	3.70	31.9	638	942	1,575	40.2	87.2	109
	5 hr. 30 min.	...	6.54	67.8	3.05	31.6	3.49	36.2	645	1,035	1,675	33.2	82.0	108
	7 hr.	...	6.57	67.0	2.83	28.9	3.74	38.1	645	1,020	1,665	33.8	82.1	101
	Injected blood		8.33	...	3.22	...	5.16	...	...	...	...	33.5	63.6	...
T 155 17.31 Kg.	Control	0	5.91	58.0	3.34	32.7	2.57	2.53	(515)	(950)	(1,525)	35.7	77.3	118
	1 hr.	173	5.73	56.8	3.25	32.0	2.53	2.48	532	983	1,515	35.2	77.7	111
	2 hr. 30 min.	398	5.54	57.2	3.00	30.9	2.54	2.63	535	1,020	1,555	31.1	75.4	105
	4 hr.	692	5.69	58.9	3.11	32.0	2.58	2.69	535	1,035	1,570	31.2	75.0	111
	5 hr. 30 min.	...	5.59	59.0	3.03	31.9	2.56	2.71	530	1,055	1,585	33.4	74.3	104
	7 hr.	...	5.50	60.2	2.94	32.2	2.56	2.80	521	1,094	1,615	32.3	73.0	101
	Injected blood		7.05	...	2.43	...	4.62	...	...	...	...	29.0	64.1	...
T 156 18.05 Kg.	Control	0	6.25	35.6	....	....	....	....	(505)	(570)	(1,075)	47.0	103.1	153
	1 hr.	136	6.19	36.9	3.99	23.8	2.20	13.1	516	596	1,112	46.4	100.0	152
	2 hr. 30 min.	340	6.05	35.7	3.85	22.7	2.20	13.0	522	590	1,112	46.9	109.0	145
	4 hr.	544	6.05	37.5	3.85	23.7	2.20	13.8	531	619	1,150	46.2	96.5	145
	5 hr. 30 min.	...	5.91	36.7	....	....	....	....	519	621	1,150	46.0	96.5	125
	7 hr.	...	6.82	38.3	3.56	23.5	2.26	14.8	542	653	1,200	45.2	92.6	125
	Injected blood		7.37	...	3.59	...	3.78	...	...	...	...	36.9	62.3	...

Protocols.—T 154: A total of 672 ec. of fluid was injected at the rate of 10 ec. per kilogram per hour into the peritoneal cavity. At the end of the experiment 475 ec. was recovered from the cavity, leaving 197 ec. that had been absorbed.

T 155: Fluid was injected into the peritoneal cavity continuously at the rate of 10 ec. per kilogram per hour, and a total of 692 ec. was injected. At the end of the experiment 370 ec. was recovered, and 322 ec. had been absorbed.

T 156: Fluid was injected into the peritoneal cavity continuously at the rate of 10 ec. per kilogram per hour, and a total of 544 ec. was given. At the end of the experiment 415 ec. was recovered, and 129 ec. had been absorbed.

TABLE 2.—*Effects of the Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity in the Presence of a Decline in Blood Pressure Produced by the Subcutaneous Injection of Histamine*

Experiment	Time from beginning	Amount of Fluid Given	Histamine, Mg.	Total Protein Blood, per Cent	Total Protein Entire from Hemoglobin and Hematocrit	Albumin Blood, per Cent Hematocrit	Albumin Entire from Hemoglobin and Hematocrit	Globulin Blood, per Cent Hematocrit	Globulin Entire from Hemoglobin and Hematocrit	Blood Volume Red Blood Cells	Blood Volume Plasma	Blood Volume Whole	Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
T 159 9.5 Kg.	Control	0	10	5.30	28.2	2.83	15.0	2.47	13.2	(302)	(532)	(834)	36.2	82.4	108
	1 hr.	95	25	5.78	29.7	3.14	16.1	2.54	13.4	311	514	825	37.8	83.3	82
	2 hr. 30 min.	238	40	5.78	29.5	-3.03	15.5	2.75	14.0	315	510	825	38.2	83.3	65
	4 hr.	380	..	5.60	27.5	2.72	13.4	2.88	14.1	323	492	815	39.7	84.3	57
	5 hr. 30 min.	..	..	5.55	27.5	2.66	13.2	2.89	14.3	317	495	812	38.0	84.7	57
	7 hr.	..	..	4.88	24.8	2.43	12.4	2.45	12.4	317	508	825	38.5	83.3	74
	Injected blood	..	..	7.40	....	2.32	....	5.18	....	..	..	..	29.7	65.2	...
T 160 12 Kg.	Control	0	10	4.71	33.0	2.49	17.4	2.22	15.6	(503)	(700)	(1,203)	41.8	89.9	100
	1 hr.	120	15	5.05	28.7	2.23	12.7	2.82	16.0	512	...	1,080	47.4	101.3	63
	2 hr. 30 min.	300	20	5.46	25.5	2.43	11.4	3.03	14.5	509	467	976	52.2	111.0	87
	4 hr.	480	..	5.55	23.4	2.32	0.78	3.23	13.6	530	422	952	55.6	115.4	93
	5 hr. 30 min.	..	..	5.68	23.3	2.60	10.7	3.08	12.7	525	411	936	56.0	117.1	116
	7 hr.	..	..	6.23	25.2	2.55	11.3	3.13	13.9	526	444	970	54.2	112.7	100
	Injected blood	..	..	....	....	3.66	....	3.17	....	..	..	..	41.5	89.3	...
T 161 10 Kg.	Control	0	10	6.23	36.0	3.62	20.9	2.61	15.8	(300)	(578)	(966)	40.4	92.0	120
	1 hr.	100	15	6.31	31.2	3.70	18.4	2.61	12.9	419	495	914	45.9	97.4	97
	2 hr. 30 min.	250	20	6.31	29.3	3.90	....	....	11.3	405	465	870	46.2	101.3	84
	4 hr.	400	45	6.50	28.2	3.79	16.9	2.60	....	408	434	842	48.5	105.6	66
	5 hr. 30 min.	..	..	6.23	24.9	3.42	15.2	2.54	9.7	420	400	820	51.2	108.7	113
	7 hr.	..	..	5.87	24.2	2.40	14.1	2.45	10.1	420	412	832	50.5	107.1	101
	Injected blood	..	..	4.37	....	2.40	....	1.88	....	..	..	..	33.4	75.0	...

Protocols.—T 159: Following the control determination 10 mg. of histamine was administered subcutaneously, and the injection of fluid into the peritoneal cavity was begun at the same time. The total amount of fluid given was, therefore, 360 cc. A total of 40 mg. of histamine was administered during the experiment. The amount absorbed was, therefore, 210 cc., and at the end of the experiment 170 cc. was recovered from the peritoneum.

T 160: Following the control determination 10 mg. of histamine was administered subcutaneously, and the injection of fluid into the peritoneal cavity was begun at the same time. The total amount of fluid given was 480 cc. The total amount of histamine given was 45 mg. of histamine given at the same time. There was no fluid absorbed, but there was a transudation of 45 cc. into the peritoneum.

T 161: Following the control determination 10 mg. of histamine was administered subcutaneously, and the injection of fluid into the peritoneal cavity was begun at the same time. The total amount of fluid given was 400 cc., and at the end of the experiment 205 cc. was recovered. The amount absorbed was, therefore, 295 cc. A total of 45 mg. of histamine was administered during the experiment.

TABLE 3.—*Effects of the Continuous Injection of Physiologic Solution of Sodium Chloride into the Peritoneal Cavity in the Presence of a Decline in Blood Pressure Produced by Graded Hemorrhage*

Experiment	Time from Beginning	Amount of Fluid Given	Amount of Blood Withdrawn	Total Protein		Albumin		Globulin		Blood Volume from Hemoglobin and Hematocrit			Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
				Blood, per Cent	Entire from Hemoglobin and Hematocrit	Blood, per Cent	Entire from Hemoglobin and Hematocrit	Blood, per Cent	Entire from Hemoglobin and Hematocrit	Red Blood Cells	Plasma	Whole			
T 157 16.68 Kg.	Control	0	106	7.14	92.4	2.83	36.6	4.31	55.8	(555)	(1,265)	(1,820)	30.0	69.1	107
	1 hr.	166	414	7.04	(93.5) 85.2	2.57	(34.4) 31.1	4.47	(59.1) 51.1	500	1,210	1,710	29.1	63.2	95
	2 hr. 30 min.	415	662	6.73	(98.2) 77.6	2.51	(36.6) 29.9	4.22	(61.5) 48.7	411	1,151	1,595	27.7	62.5	103
	4 hr.	644	...	6.45	(102.6) 70.0	2.51	(39.5) 27.2	3.94	(62.7) 42.8	370	1,085	1,455	25.3	57.9	76
	5 hr. 30 min.	...	...	6.32	(101.2) 68.6	2.38	(38.1) 25.8	3.94	(67.7) 42.8	370	1,055	1,455	25.1	57.9	61
	7 hr.	...	...	6.41	(88.2) 55.6	2.43	(33.4) 21.1	3.98	(51.4) 31.5	377	853	1,235	30.6	63.2	65
T 158 13.5 Kg.	Control	0	135	6.70	46.0	4.02	27.7	2.68	18.3	(452)	(688)	(1,140)	39.6	89.2	132
	1 hr.	135	337	6.41	(43.6) 38.1	3.88	(26.3) 23.0	2.53	(17.2) 15.1	411	591	1,005	40.9	88.2	114
	2 hr. 30 min.	338	540	6.14	(45.9) 32.8	3.39	(26.0) 18.1	2.75	(19.9) 14.7	330	531	861	33.2	82.0	125
	4 hr.	510	...	5.97	(47.3) 26.5	3.42	(27.3) 15.2	2.55	(19.8) 11.3	243	444	687	35.4	79.0	80
	5 hr. 30 min.	...	...	5.73	(47.2) 26.4	3.42	(29.9) 15.8	2.31	(19.1) 10.6	256	460	716	35.3	75.8	61
	7 hr.	...	...	5.64	(47.5) 26.7	3.25	(27.5) 15.4	2.39	(19.8) 11.3	213	473	716	31.0	75.8	51

Protocols.—T 157: Following the control determination 106 cc. of blood was withdrawn; at the end of two and a half hours another 248 cc. was withdrawn. An equivalent amount of fluid was injected continuously intraperitoneally at the rate of 10 cc. per kilogram per hour, beginning simultaneously with the initial withdrawal of blood. A total of 644 cc. of fluid was given, and at the end of the experiment 420 cc. was recovered. The amount of fluid absorbed was 224 cc.

T 158: Following the control determination 135 cc. of blood was withdrawn; at the end of one hour 202 cc. was withdrawn, and at the end of two and a half hours another 248 cc. was withdrawn. An equivalent amount of fluid was injected continuously into the peritoneal cavity at the rate of 10 cc. per kilogram per hour beginning simultaneously with the initial withdrawal of blood. A total of 540 cc. of fluid was given, and at the end of the experiment 297 cc. was recovered. The amount of fluid absorbed was 243 cc.

TABLE 4.—Effects on the Composition of the Blood of Introduction of Physiologic Solution of Sodium Chloride into the Stomach

Experiment	Time from Beginning	Amount of Fluid Given	Total Protein		Albumin		Globulin		Blood Volume from Hemoglobin and Hematocrit			Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
			Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Blood, per Cent Hematocrit	Entire from Hemoglobin and Hematocrit	Red Blood Cells	Plasma	Whole			
T 162 16.75 Kg.	Control	0	6.47	57.4	2.89	25.6	3.58	31.8	(573)	(887)	(1,460)	39.3	88.2	138
	1 hr.	167	6.64	55.1	3.11	25.8	3.53	29.3	505	830	1,425	41.7	90.5	117
	2 hr. 30 min.	412	6.82	58.0	3.23	27.4	3.59	30.6	590	850	1,440	41.1	89.3	135
	4 hr.	668	6.55	52.4	3.31	26.5	3.24	25.9	570	800	1,370	41.6	93.8	135
	5 hr. 30 min.	...	6.47	59.5	3.06	28.1	2.41	31.4	595	920	1,515	40.3	85.2	108
	7 hr.	...	6.28	57.7	2.72	24.9	3.56	32.8	621	918	1,539	40.0	84.3	117
	Injected blood		6.64	...	2.21	...	4.43	...	...	...	...	29.3	66.3	...
T 163 10.15 Kg.	Control	0	6.50	59.2	...	...	...	...	(640)	(1,065)	(1,705)	37.5	79.0	145
	1 hr.	191	5.82	53.1	...	...	...	...	618	912	1,530	40.3	83.2	125
	2 hr. 30 min.	473	6.09	54.6	...	...	...	...	649	896	1,545	42.0	87.2	130
	4 hr.	704	5.87	53.4	...	...	...	...	650	910	1,560	41.8	86.2	144
	5 hr. 30 min.	...	5.87	49.2	...	...	...	...	642	838	1,480	43.5	90.9	140
	7 hr.	...	6.12	47.1	...	...	...	...	650	770	1,420	45.8	94.9	135
	Injected blood		5.41	...	...	...	...	...	...	...	...	24.8	50.0	...
T 164 12.9 Kg.	Control	0	6.17	38.8	3.85	24.1	2.32	14.7	(497)	(628)	(1,125)	44.2	95.5	132
	1 hr.	129	6.32	37.2	3.65	21.5	2.67	15.7	495	588	1,083	45.7	99.3	137
	2 hr. 30 min.	323	6.43	37.0	3.62	20.7	2.81	16.3	503	572	1,075	46.8	100.0	133
	4 hr.	516	6.28	34.7	3.77	20.8	2.51	13.9	508	552	1,060	47.9	101.3	126
	5 hr. 30 min.	...	6.37	35.3	3.60	20.0	2.77	15.3	505	555	1,060	47.7	101.3	106
	7 hr.	...	6.10	36.3	3.39	20.2	2.71	16.1	501	595	1,096	45.7	98.0	102
	Injected blood		7.1	...	3.14	...	3.96	...	...	...	...	32.0	79.0	...

Protocols.—T 162: Fluid was run into the stomach continuously through a stomach tube, at the rate of 10 cc. per kilogram per hour. A total of 688 cc. was given. At the end of the experiment 110 cc. was found in the stomach. The dog vomited 70 cc. at the end of the second hour.

T 163: A total of 764 cc. of fluid was placed in the stomach during the experiment; one-half was run in at the beginning, and the other half at the end of two hours. At the end of the experiment 385 cc. of fluid remained in the stomach and 110 cc. was found in the peritoneal cavity. The dog did not vomit.

T 164: A total of 516 cc. of fluid was placed in the stomach during the experiment; one-half was run in at the beginning, and the other half at the end of two hours. At the end of the experiment 36 cc. of fluid remained in the stomach. The dog did not vomit.

TABLE 5.—*Effects of Introduction of Physiologic Solution of Sodium Chloride into the Stomach in the Presence of a Decline in Blood Pressure Produced by the Subcutaneous Injection of Histamine*

Experiment	Time from Beginning	Amount of Fluid Given	Histamine, Mg.	Total Protein		Albumin		Globulin		Blood Volume from Hemoglobin and Hematocrit			Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
				Blood, per cent Hematocrit	Entire from Hemoglobin and Hematocrit	Blood, per cent Hematocrit	Entire from Hemoglobin and Hematocrit	Blood, per cent Hematocrit	Entire from Hemoglobin and Hematocrit	Red Blood Cells	Plasma	Whole			
T 167 15.6 Kg.	Control	0	0	7.32	61.4	4.21	35.2	3.11	26.2	(675)	(838)	(1,513)	41.7	102.7	125
	1 hr.	150	30	7.37	47.5	4.16	27.8	3.21	20.7	722	641	1,366	52.9	113.6	93
	2 hr. 30 min.	390	65	7.63	44.5	4.21	24.6	3.42	19.9	712	531	1,226	56.0	117.1	85
	4 hr.	624	125	7.19	42.9	4.01	24.1	3.15	18.8	753	597	1,350	55.8	115.4	81
	5 hr. 30 min.	..	..	7.50	44.8	4.13	24.7	3.37	20.1	793	597	1,390	57.0	111.9	115
	7 hr.	..	..	7.70	46.0	4.8	25.0	2.99	21.0	792	598	1,390	56.9	111.9	102
	Injected blood			6.46	...	1.07	...	5.40	...	...	...	.....	33.1	72.0	...
T 168 17.7 Kg.	Control	0	0	6.13	44.0	4.75	34.1	1.38	9.9	(573)	(717)	(1,290)	11.5	91.0	119
	1 hr.	177	60	6.24	34.7	4.97	27.6	1.27	7.1	561	556	1,120	50.3	104.9	90
	2 hr. 30 min.	443	80	5.92	35.9	4.52	27.4	1.40	8.5	551	609	1,160	47.8	101.3	65
	4 hr.	698	120	6.00	30.1	4.52	26.0	1.44	9.2	564	596	1,160	18.6	101.3	83
	5 hr. 30 min.	..	..	6.28	34.2	4.66	25.3	1.62	8.9	551	514	1,095	50.3	107.1	103
	7 hr.	..	..	6.14	32.3	4.50	23.7	1.64	9.6	569	526	1,095	52.0	107.1	101
	Injected blood			6.96	...	2.83	...	4.13	...	...	...	.....	29.0	62.5	...

Protocols.—T 167: A total of 624 cc. of fluid was placed in the stomach, one-half at the beginning of the experiment and the other half two hours later. Following the control determinations 10 mg. of histamine was administered, and enough thereafter to keep the blood pressure depressed. At the end of the experiment 550 cc. of fluid was found in the stomach. There was no vomiting.

T 168: A total of 700 cc. of fluid was placed in the stomach, one-half at the beginning of the experiment and the other half two hours later. Following the control determinations 10 mg. of histamine was administered, and enough thereafter to keep the blood pressure depressed. At the end of the experiment 550 cc. of fluid was found in the stomach. There was no vomiting.

TABLE 6.—*Effects of Introduction of Physiologic Solution of Sodium Chloride into the Stomach in the Presence of a Decline in Blood Pressure Produced by Graded Hemorrhage*

Experiment	Time from Beginning	Amount of Fluid Given	Amount of Blood Withdrawn	Total Protein		Albumin		Globulin		Blood Volume from Hemoglobin and Hematocrit			Hematocrit	Hemoglobin	Mean Blood Pressure, Mm. Hg
				Blood, per Cent	Entire from Hemoglobin and Hematocrit	Blood, per Cent	Entire from Hemoglobin and Hematocrit	Blood, per Cent	Entire from Hemoglobin and Hematocrit	Red Blood Cells	Plasma	Whole			
T 165	Control	0	127	5.91	46.1	3.70	28.8	2.21	17.3	(456)	(780)	(1,236)	36.9	79.0	115
12.7 Kg.	1 hr.	127	317	5.54	(48.9) 44.2	3.42	(30.4) 27.3	2.12	(18.7) 16.9	392	798	1,190	32.6	73.5	98
	2 hr. 30 min.	318	417	5.58	(40.2) 36.9	3.48	(30.1) 23.0	2.00	(18.4) 13.9	350	660	1,010	34.6	72.8	88
	4 hr.	508	...	5.80	(49.4) 33.3	3.50	(29.5) 20.1	2.30	(19.1) 13.2	309	574	883	35.0	75.0	62
	5 hr. 15 min.	...	...	5.50	(49.8) 33.7	3.37	(29.7) 20.3	2.22	(19.3) 13.4	311	603	914	34.0	72.5	29
T 166	Control	0	121	7.14	42.7	4.67	28.0	2.47	14.7	(539)	(599)	(1,138)	47.4	105.6	132
12.1 Kg.	1 hr.	121	276	7.68	(43.4) 38.9	4.61	(26.3) 23.3	3.07	(17.1) 15.7	496	506	1,002	49.5	107.1	133
	2 hr. 30 min.	303	...	7.56	(43.9) 33.4	4.53	(26.6) 20.0	3.03	(17.3) 13.4	417	442	859	48.5	105.6	70
	4 hr.	484	...	7.41	(42.4) 31.9	4.50	(25.9) 19.3	2.91	(16.5) 12.6	417	430	847	49.2	107.1	76

Protocols.—T 165: A total of 508 cc. of fluid was given into the stomach, 254 cc. at the beginning of the experiment and 254 cc. at the end of the second hour. Blood was withdrawn at intervals to equal 10 cc. per kilogram per hour. The third bleeding in the experiment was of 100 cc. which produced such a profound fall in pressure that the full amount could not be taken. Blood pressure declined gradually from this point, and the animal died at the end of five hours and forty-five minutes. The amount of fluid found in the stomach was 525 cc., while only 508 cc. had been injected.

T 166: In this experiment, the animal tolerated only two hemorrhages, 121 cc. at the beginning of the experiment and 155 cc. at the end of the second hour. This dog died in four and a half hours. The total fluid placed in the stomach was 484 cc., and 425 cc. was recovered at the end of the experiment.

was found in the stomach of these dogs at the end of the experiment as was placed in them during the experimental period. The results of these experiments are given in table 5.

C. When the Blood Pressure Is Caused to Decline as the Result of Hemorrhage: It is perhaps significant that the animals in these two experiments neither tolerated the withdrawal of 10 cc. of blood per kilogram per hour for four hours nor lived through the usual seven hours of the experiments. The absolute amount of plasma protein in the circulation decreased, but this loss was accounted for by the protein in the withdrawn blood. The percentage of protein per unit volume of· serum remained practically constant. The volume of blood plasma decreased rather markedly. Almost all of the fluid placed in the stomachs of these dogs was recovered at the end of the experiments. The results of these experiments are shown in table 6.

<div align="center">COMMENT</div>

The usual methods by which fluids are administered are intravenously, subcutaneously, intraperitoneally, by mouth and by rectum. In previous studies,[1] the effects on the composition of the blood of the administration of various fluids intravenously and of physiologic solution of sodium chloride subcutaneously to animals with a normal blood pressure and to those in which a decline in blood pressure had been produced by several means were determined. Particular emphasis has been placed on alterations in the percentage and absolute amounts of plasma protein, because protein maintains to a large degree the osmotic pressure of the blood stream. It has been shown previously [6] that the fluid that escapes from the blood stream as a result of trauma to the intestines, mild trauma to an extremity and burns has approximately the same protein content as the plasma of the blood stream. The introduction of physiologic solution of sodium chloride intravenously and of most of the other solutions frequently used in the treatment of shock caused little alteration in the composition of the blood when injected into dogs with normal blood pressures. When a decline in blood pressure was produced by hemorrhage and fluids were injected intravenously, the loss of protein was limited to that removed in the withdrawn blood. On the contrary, the intravenous injection of fluid into animals in which gross capillary injury had been inflicted by either mechanical or chemical means resulted in a loss of most of the fluid that was injected and in addition, in a decrease in the percentage of protein in the plasma remaining in the blood vessels. When salt solution was injected subcutaneously

6. Beard, J. W., and Blalock, A.: Experimental Shock. VIII. The Composition of the Fluid that Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines and After Burns, Arch. Surg. **22**:617 (April) 1931.

into normal animals, there was little alteration in the composition of the blood. The subcutaneous injection of physiologic solution of sodium chloride into animals from which blood was removed was not associated with any additional loss of protein. In some instances there was a slight increase in the absolute amount of plasma protein if correction is made for the amount removed. When the subcutaneous injection of salt solution was accompanied by injury to large areas of capillaries, there was a large loss of protein from the circulation but that remaining was not diluted greatly, as was found in the experiments in which the fluid was given intravenously.

The results of the present experiments in which physiologic solution of sodium chloride was injected into the peritoneal cavity are similar to those that were obtained in the studies in which the fluid was injected subcutaneously. If any difference is present, it is in favor of the more rapid absorption by the blood stream of the fluid that was placed in the peritoneal cavity.

When, however, the salt solution was placed in the stomach, the results were similar to those obtained when no fluid was administered by any route. Studies of the composition of the blood indicated little if any absorption of the fluid that was placed in the stomach. It is possible that the morphine that was used as the anesthetic might have diminished the absorption of the fluid.

SUMMARY

The effects on the composition of the blood of the introduction of physiologic solution of sodium chloride intraperitoneally and by stomach tube into normal dogs and into dogs in which a decline in blood pressure was produced by hemorrhage and by histamine have been determined. The studies included determinations of the arterial blood pressure, the percentage of hemoglobin, the concentration of the red blood cells, the volumes of whole blood, red blood cells and plasma, and the percentages of total protein, albumin and globulin in the blood serum.

The introduction of physiologic solution of sodium chloride into the peritoneal cavity of the normal dog was associated with an increase in the volume of plasma, a slight dilution of the protein of the plasma and a small increase in the absolute amount of plasma protein. When the blood pressure was caused to decline by giving histamine subcutaneously and salt solution was injected into the peritoneal cavity, there was a diminution in the volume of plasma and in the absolute amount of plasma protein. The percentage of protein per unit volume of plasma changed very little. The removal of blood and the introduction of salt solution intraperitoneally were associated with decreases in the plasma volume and in the absolute amount of plasma protein. However, the

losses of protein and plasma were less than the amounts removed in the blood. There was a slight dilution of the protein remaining in the circulation. The findings in these experiments in which the fluid was introduced intraperitoneally were similar to those obtained following the subcutaneous injection of solution.

The experiments in which physiologic solution of sodium chloride was introduced by stomach tube into normal dogs and into dogs with a low blood pressure showed no appreciable effects of the administration of fluid.

ABSORPTION OF DEXTROSE FROM THE COLON

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The ease with which fluids can be introduced through the rectum into the colon has resulted in the widespread use of this method for the administration of a variety of substances. There is undoubtedly a paucity of evidence from carefully controlled experiments on the ability of the colonic mucous membrane to absorb protein, fat or carbohydrate. It is well known that the rectal administration of ether results in general anesthesia. More recently the success with which narcosis may be produced by the rectal administration of sodium amytal and avertin proves that fairly complicated molecules may be absorbed by the mucosa of the large bowel. The sedative effect produced by the colonic administration of chloral hydrate or sodium bromide is a well established clinical phenomenon. The bromide ion, when administered rectally in sufficient amounts, can be recovered from the urine, the sweat and the lacrimal secretions. Recently, Cohn,[1] in this laboratory, found that iodine is readily absorbed from the colon.

The nutritive substance most often given either by rectal drip or by massive colonic instillation is dextrose. It supplies a variety of needs in the body economy. The evidence of its utilization when given into the large bowel has until recently been rather meager. Every textbook of therapeutics stresses the efficacy of administering dextrose by rectum to those patients requiring carbohydrates in instances in which the oral route cannot be used. No chapter on diabetes misses the opportunity of mentioning that dextrose may be administered by proctoclysis when necessary. In most surgical clinics the method has been used whenever the use of dextrose has been indicated and its administration by any other route has been inadvisable. The evidence on the total caloric value of the dextrose that can be absorbed from the large bowel is quite indefinite.

1. Cohn, B. N. E.: The Absorption of Compound Solution of Iodine from the Gastro-Intestinal Tract with Special Reference to Absorption of Free Iodine, Arch. Int. Med. **49**:950 (June) 1932.

Recently, experimental data published by McNealy and Willems [2] and by Scott and Zweighaft [3] question the ability of the large bowel to absorb dextrose. The experiments of McNealy and Willems were carried out on the colon of the dog. The large rectal ampulla was not utilized. Because of this, similar experiments have been performed, the entire colon and rectum being used—a method employed by Goldschmidt and Dayton [4] in their sodium chloride experiments. These studies have been extended to include a study of the degree to which the pancreatectomized dog with hyperglycemia and the hypoglycemic animal will absorb dextrose from the same portion of the alimentary tract. It is hoped that the present experiments will enhance our knowledge of the advisability and efficacy of administering dextrose by the rectal route as a therapeutic measure in the diabetic and non-diabetic patient. The step from the laboratory animal to the human patient is not so great but that some comparisons can be drawn.

REVIEW OF THE LITERATURE

The early literature is replete with a variety of mixtures which were supposedly efficacious in maintaining life when given by the rectal route. How trustworthy these reports are cannot be stated.

Voit and Bauer [5] performed the first systematic research on the absorptive mechanism of the colon. Their experiments were performed with albumin, and they stated that the addition of sodium chloride assisted in the absorption of that substance. Czerny and Latschenberger [6] reported studies on two patients in whom the entire large intestine, or part of it, had been completely cut off from the small intestine. In these they obtained evidence which indicated that dextrose was absorbed. Deucher [7] reported that he gave five enemas to a patient during nineteen hours, each containing 40 Gm. of dextrose. One hundred and fifty-four grams of dextrose was absorbed, constituting 77 per cent of the amount introduced. Reach,[8] experimenting with normal men, found that there was a slight rise in the respiratory quotient, which corresponded to a rise in the peripheral blood sugar after the rectal administration of dextrose. He assumed that there was

2. McNealy, R. W., and Willems, J. D.: Surg., Gynec. & Obst. **49**:794, 1929.

3. Scott, E. L., and Zweighaft, J. F. B.: Blood Sugar in Man Following the Rectal Administration of Dextrose, Arch. Int. Med. **49**:221 (Feb.) 1932.

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5. Voit, C., and Bauer, J.: Ztschr. f. Biol. **5**:537, 1869.

6. Czerny, von V., and Latschenberger, J.: Virchows Arch. f. path. Anat. **59**:161, 1874.

7. Deucher, P.: Deutsches Arch. f. klin. Med. **58**:210, 1897.

8. Reach, F.: Arch. f. exper. Path. u. Pharmakol. **47**:231, 1902.

some absorption of dextrose. Zehmisch,[9] working with human beings, gave 152 Gm. of dextrose by rectum and lost 103 Gm. (67.5 per cent), supposedly by absorption. Arnheim [10] gave 50 Gm. of dextrose by *bowel to diabetic persons.* He was able to recover only 3 Gm. of dextrose after a period of five hours. He did not believe that bacterial action could account for the dextrose that had disappeared. Boyd and Robertson [11] fed seven women on nutrient enemas for from six to seven days. Each day the bowel was washed out and the contents analyzed. Urinary nitrogen was used as a gage of the absorption of nitrogenous substances. They reported that in two cases 100 per cent of the introduced dextrose was absorbed. They lost as much as 61.8 and 81 Gm. of dextrose during twenty-four hours, but recovered the bulk of the protein in the rectal washings. After having incubated dextrose solutions which were contaminated with colon bacilli, they concluded that the dextrose lost by bacterial action was insignificant. They were not able to produce dextrosuria with the amounts they administered. Halasz,[12] working with patients, placed clysters in the large bowel and, in from five to six hours, found that from 50 to 200 Gm. of the dextrose had disappeared. He accounted for only from 0.5 to 1 per cent of the dextrose as lost by bacterial action. Mutch and Ryffell [13] gave four enemas to each of several patients during a twenty-four hour period. Each enema consisted of 450 cc. of 6 per cent dextrose. When the nutrient enemas were well tolerated, they increased the dextrose to 60 Gm. to the pint of solution. Using a "washout" method of experimentation, they concluded that dextrose could be satisfactorily administered by this route to a maximum of 700 calories *per day.* Hari and Halasz,[14] *working with dogs,* placed a ligature around the ileocecal valve and, after the introduction of dextrose solution into the rectum, found that the respiratory quotient was nearly always increased. They reported that they were able to produce actual dextrosuria after the rectal administration of dextrose to their animals. Tallerman [15] gave dextrose enemas to seven normal persons and to one patient with functional vomiting. The solution consisted of 60 Gm. of dextrose in 180 cc. of physiologic solution of sodium chloride, or a 33 per cent dextrose solution. He concluded that absorption took place uniformly, the maximum rise in blood sugar occurring in about one

9. Zehmisch, F.: Ausnutzung von Nährklystieren, Halle, C. Nietschmann, 1903.

10. Arnheim, J.: Ztschr. f. diätet. u. phys. Therap. **8**:75, 1905.

11. Boyd, F. D., and Robertson, T.: Scottish M. & S. J. **18**:193, 1906.

12. Halasz, A. V.: Deutsches Arch. f. klin. Med. **98**:433, 1910.

13. Mutch, N., and Ryffell, J. H.: Guy's Hosp. Rep. **66**:223, 1912.

14. Hari, P., and Halasz, A. V.: Biochem. Ztschr. **88**:337, 1918.

15. Tallerman, K. H.: Quart. J. Med. **13**:356, 1919-1920.

hour and twenty minutes with an average rise of 30 mg. per hundred cubic centimeters of blood. Varela and Rubino [16] stressed the necessity of exposing the dextrose solution to the rich venous plexus of the rectal ampulla. They placed 40 per cent dextrose solutions in the rectums of patients and tested the peripheral blood and urine for dextrose. They found that minute amounts were absorbed shortly after the dextrose was introduced, but that soon the colon became irritated and expelled the enema. Carpenter,[17] in two experiments on human beings, gave 30 Gm. of dextrose in 500 cc. of physiologic solution of sodium chloride. Within two or three hours after the injection, the respiratory quotient changed from 0.02 to 0.05. He found that 17.5 Gm. of dextrose was absorbed in one instance and, in the other, 26.3 Gm. Similarly, five hours after the administration of 60 Gm. of dextrose, he found that 34.6 Gm. had apparently been absorbed. The quantitative results were based on the "washout" method, using more than one lavage.

Bingel [18] investigated the absorption of dextrose in diabetic patients. He concluded that only small amounts of dextrose were absorbed. One hour after having placed 35 Gm. of dextrose in the bowel, 31 Gm. was recovered in the stool. Bingel incubated fecal material with added dextrose, and claimed that the dextrose lost was almost as great as that supposed to have been absorbed.

Franke and Wagner [19] gave concentrated enemas to dogs. They used 25 Gm. of dextrose in a 50 per cent solution. They determined the peripheral blood sugar at fifteen, thirty, forty-five and sixty minute intervals, and found the highest rise of blood sugar to be 20 mg. per hundred cubic centimeters. They concluded that dextrose enemas had little, if any, effect on the peripheral blood sugar. Levi [20] gave dextrose to fasting normal, diabetic and postoperative patients. He used 500 cc. of from 10 to 16 per cent dextrose solutions and found that patients varied as to their reaction, but, in general, took up only slight amounts of the dextrose.

McNealy and Willems, in 1929, working with isolated loops of the large and small bowel of the dog, gave this problem renewed interest. They introduced known amounts of dextrose into the colon or ileum and studied the changes quantitatively. They also studied the ileal, colic and peripheral venous blood sugar during the experiment. They used a 5 per cent dextrose solution and found that from 0.3 per cent

16. Varela and Rubino: Med. Klin. **18**:831, 1922.

17. Carpenter, T. M.: Human Metabolism with Enemata of Alcohol, Dextrose, and Levulose, publ. 369, Washington, D. C., Carnegie Institution, 1925.

18. Bingel, A.: Therap. d. Gegenw. **46**:436, 1905.

19. Franke, W., and Wagner, R. J.: J. Metab. Research **6**:375, 1924.

20. Levi, D.: Brit. J. Surg. **15**:282, 1927.

to as much as 2.6 per cent of the dextrose was lost from the large bowel, with a corresponding loss of from 23.3 to 59 per cent from the ileum over the same time interval. They found that the colic venous blood sugar fell, while the blood sugar from the ileal vein in the ileal experiments rose. They concluded that a 5 per cent dextrose solution was of little or no nutritional value when administered rectally. They suspected the presence of an incompetent ileocecal valve as the basis for some of the experimental and clinical success reported in the literature. Later,[21] they reported the effect of sodium chloride on dextrose absorption from the colon and found that, although the percentage of absorption was slightly greater, it was not sufficient to be of practical importance.

Pressman [22] gave 33 per cent dextrose solutions by rectum and by mouth to human beings and observed the blood sugar curves for a period of four hours. He found that the peripheral blood sugar level fell after the introduction of dextrose into the rectum without any significant preliminary rise. He recovered an average of 24 per cent from the colon after four hours. He stated that 90 per cent of the dextrose was destroyed by incubation with feces in seven hours. De Takáts,[23] in 1931, gave 1,000 cc. of 5 per cent dextrose to patients under the skin, by mouth and by bowel. The blood sugar level rose after introduction of dextrose under the skin and by mouth. When the dextrose was given by rectum, the blood sugar fell during a period of two hours. He noted that no dependence could be placed on the amount absorbed by rectum, and that insulin reactions occurred when this method of entry was depended on in the diabetic person.

Scott and Zweighaft, in experiments on medical students, investigated the blood sugar changes following the rectal administration of dextrose. They found no rise in the peripheral blood sugar after the administration of 180 cc. of a 15 or 30 per cent solution of dextrose. They also found that, after the rectal introduction of 200 cc. of a 10 per cent dextrose solution, the blood sugar level fell about 10 mg. per hundred cubic centimeters, while after the administration of 400 cc. of a 10 per cent dextrose solution the fall was about 7.5 mg. per hundred cubic centimeters. They concluded that the fall in blood sugar was due to pancreatic action or chance variation. They were able to recover from 25 to 50 per cent of the dextrose they had administered.

Since this paper went to press, Perusse [23a] has published data that led him to make the following statement: "We can then perhaps come

21. McNealy, R. W., and Willems, J. D.: The Absorption of Dextrose from the Colon: II. A Study of the Effects of Chemical Excitants and of Stimulants of Dextrose Enema, Arch. Surg. **22**:649 (April) 1931.

22. Pressman, J. J.: Am. J. M. Sc. **179**:520, 1930.

23. de Takáts, G.: Am. J. Surg. **11**:39, 1931.

23a. Perusse: Surg., Gynec. & Obst. **54**:770, 1932.

to the tentative conclusion that 1 per cent glucose solution is the ideal for restoring water balance and for supplying some degree of nutrient."

COMMENTS ON PREVIOUS EXPERIMENTAL AND CLINICAL OBSERVATIONS

There are certain obvious objections to the methods used by some of the investigators whose work has been cited. The "washout" method has been widely criticized on the ground that it fails to consider adequately: (1) bacterial action on the introduced dextrose; (2) the fact that reverse peristalsis may carry the solution beyond the reach of recovery, or even through an incompetent ileocecal valve into the ileum where absorption may occur.

Recent investigations of the responsibility of bacterial action for the loss of some of the dextrose from the large bowel give contradictory results. Cori,[24] in 1925, incubated the small intestines with known contained quantities of dextrose for from three to five hours at 37 C., and he concluded that the amount of dextrose lost in this part of the bowel by bacterial action was so small that it was negligible. Bingel [18] incubated fecal material with dextrose and claimed that the quantity lost through bacterial action was equal to the amount supposed to have been absorbed. Pressman [22] incubated dextrose and feces for seven hours. He found that nearly 90 per cent of the dextrose had been destroyed. McNealy and Willems [2] avoided the question of loss of dextrose in this manner by using a short period of experimentation.

Experimental and clinical data demonstrate that the incompetency of the ileocecal valve may play a large part in those instances in which absorption has been demonstrated. Cannon [25] found that large injections into the colon go into the small intestine by means of antiperistalsis. Case [26] stated that the true cause of insufficiency of the ileocecal valve is overdistention of the right half of the colon. He • found insufficiency in one sixth of 1,500 cases of constipation, observed roentgenologically. A personal communication from Pendergrass [27] supports this observation.

Other methods for the solution of the problem of dextrose absorption have been offered. Salvesen [28] reported a fall in the inorganic phosphates following injection of dextrose into the blood stream. Bollinger and Hartman [29] and Harrop and Benedict [30] have also

24. Cori, C. F.: J. Biol. Chem. **66**:691, 1925.
25. Cannon, W. B.: Am. J. Physiol. **6**:251, 1902.
26. Case, J. T.: Arch. Roentgen Ray **19**:375, 1915.
27. Pendergrass, E. P.: Personal communication.
28. Salvesen, H. A.: J. Biol. Chem. **56**:443, 1923.
29. Bollinger, A., and Hartman, F. W.: J. Biol. Chem. **64**:91, 1925.
30. Harrop, G. A., Jr., and Benedict, E. M.: J. Biol. Chem. **59**:683, 1924.

reported changes in the inorganic phosphates of the serum after injections of dextrose. I am not aware that the level of blood inorganic phosphates has been used as a measure of the absorption of dextrose from the colon. The use of the respiratory quotient in this type of experiment is open to some question unless the results are striking. Brodie,[31] in 1910, demonstrated that the introduction of distilled water into the bowel might cause increased oxygen consumption.

Diabetic patients show a marked variation in the readiness with which the liver glycogen may be mobilized in response to nervous stimulation and to mechanical pressure changes in the intestinal tract. This factor, as brought out by Smith[32] in 1930, may influence the respiratory quotient. Furthermore, the sensitive patient may show a slight rise in the sugar in the blood from the mere insertion of a rectal tube with a later and more marked rise in the blood sugar if the amount of solution introduced into the rectum is sufficient to cause marked distention of the intestine. This reversal of glycogen synthesis may be responsible for the increase in the respiratory quotient noted.

So far as I have been able to ascertain from a careful search of the literature, no one whose experiments have been controlled has found the marked alterations of the peripheral venous blood sugar after the rectal administration of dextrose which are encountered when dextrose is given by mouth.

Cori,[33] after investigation of the alimentary absorption of dextrose, has concluded recently that the peripheral blood sugar curve is not a measure of intestinal absorption. Magee and Reid,[34] on the contrary, have concluded that the dextrose curve is an index of intestinal absorption. They compared the portal and systemic blood during the absorption of dextrose from the intestine and found that the pre-absorption values were practically always identical, but that about three minutes after the ingestion of the solution the portal blood sugar had risen about 20 mg. higher than the systemic blood sugar. These relative positions were approximately maintained until the end of the experiment. They assumed that the difference between the curves could be interpreted to represent the balance between the effects of hepatic function and of tissue metabolism on the blood sugar, and the systemic (venous) curve afforded as good an index of the rate of absorption as the portal curve.

31. Brodie, T. G.; Cullis, W. C., and Halliburton, W. D.: J. Physiol. **40**:173, 1910.

32. Smith, B.: California & West. Med. **33**:857, 1930.

33. Cori, C.: Physiol. Rev. **11**:143, 1931.

34. Magee, H. E., and Reid, E.: J. Physiol. **73**:163, 1931.

The strength of the solution used in the bowel in attempting to demonstrate absorption has varied considerably. Goldschmidt [35] observed that the absorption from the entire length of the intestinal tract, so far as sodium chloride was concerned, involved a similar mechanism, and that the mechanism could be qualitatively explained by the known laws of osmosis. Theoretically, a 4.9 per cent dextrose solution has the same osmotic tension as physiologic solution of sodium chloride. Hausman [36] demonstrated that hypertonic solutions may produce undesirable results. He caused death in rats through the withdrawal of large quantities of water into the peritoneal cavity by means of a 50 per cent solution of dextrose. Certain of the variations in the results of different investigators may be explained by the difference in the concentrations of dextrose which were used.

In consideration of the literature and experimental data covered in this résumé, an experiment on the problem of dextrose absorption from the intestinal tract in the normal, the pancreatectomized and the insulinized animal was outlined which:

(1) Eliminated the ileum and isolated the colon and rectum.

(2) Considered the absorption of isotonic as well as hypertonic dextrose solution in the normal dog and isotonic dextrose solutions in the pancreatectomized, hyperglycemic, and in the insulinized, hypoglycemic, dog.

(3) Eliminated the possibility of intestinal putrefaction or bacterial action as a great factor in the loss of dextrose by careful cleansing of the bowel and by limiting the time of the experiment.

(4) Measured the absorption of dextrose in three ways simultaneously:
    (*a*) recovery and washings
    (*b*) peripheral blood sugar studies
    (*c*) colonic blood sugar studies

(5) Was controlled in the following ways:
    (*a*) Similar experiments were made with loops of ileum of equal length where dextrose absorption is known to take place.
    (*b*) An inert substance (paraffin oil) was introduced into the colon and rectum to control possible alterations in the blood sugar due to mere filling of the bowel.
    (*c*) Loss of dextrose through bacterial action and mere handling was determined by the incubation of a known dextrose solution within a colon and rectum removed from a freshly killed animal, washed and prepared in a similar manner over the same time period.
    (*d*) The possible presence of large amounts of nondextrose copper-reducing substances was eliminated by the introduction of distilled water into the colon and rectum under like methods and titration of the recovered solution by the same method used in the colonic dextrose determinations.

35. Goldschmidt, S.: Physiol. Rev. **1**:421, 1921.
36. Hausman, W.: Wien. klin. Wchnschr. **38**:332, 1925.

EXPERIMENTAL METHOD

In the experimental work twenty-four dogs were used. They were of mongrel breeds, and weighed from 7 to 32 Kg. The average weight was about 10 Kg. All dogs received their last feedings at 4 o'clock on the day before the experiment. Sodium amytal (sodium iso-amyl ethyl barbiturate) anesthesia was employed, 50 mg. per kilogram of body weight being introduced intraperitoneally. Nearly all the dogs went to sleep without excitement and slept quietly throughout the entire experiment with deep, slow respiration, although there was an occasional exception to this.

The abdomen was opened, and the appendix with the adjacent ileum was mobilized and brought into the wound. Two ligatures were passed around the ileum at its cecal junction and tightly tied. The tip of the appendix was then removed, and a glass cannula with an attached fenestrated rubber tube was inserted through the appendix into the cecum. The fenestrated rubber tube prevents collapse of the bowel for a distance of about 3 inches. Two ligatures were used to fasten the stump of the appendix about the cannula. Another rubber tube was attached to the end of the cannula which projected from the appendical stump.

The colon was washed out throughly by running warm tap water into the appendical cannula by means of a funnel. When the water coming from the rectum was clear, a tube similar to that in the cecum was inserted into the rectum. Leakage around the tube was prevented by means of a purse-string suture placed in the rectal sphincter. The colon was again flushed with warm tap water. Any fluid remaining was then forced out by gently passing air through the appendical cannula and elevating the head of the table. The operative procedure rarely took longer than thirty minutes.

Specimens of blood were taken from one of the veins draining the colic blood and from the exposed femoral vein. After the colon was carefully evacuated so that the bowel was collapsed, the rectal tube was clamped, and a dextrose solution of desired strength and known amount was allowed to run into the system at a pressure not exceeding 150 mm. of the solution. When the bowel appeared to be full, but not unduly distended, the appendical clamp was closed. The quantity of solution introduced varied with the size of the animal, 158 and 238 cc. being the lowest and highest amounts used. All solutions were warmed to 38.5 C. before being placed in the bowel. The abdominal incision was then closed, the appendical cannula extending through the closed wound.

Specimens of blood from the femoral vein were taken at half hour intervals. At the end of two hours the last specimen was taken, the abdomen again opened, and a specimen withdrawn from the colic vein. Difficulty in the control of hemorrhage from the colic vessel prevented the withdrawal of blood at more frequent intervals. Following the collection of the blood specimens, the solution remaining within the bowel was forced through the rectal cannula into a beaker by means of air. The head of the table was again elevated in order to facilitate the recovery of fluid. The bowel was flushed with 250 cc. of distilled water, this solution also being forced out into a second beaker by means of air and elevation of the head of the table. It is of interest that, of the 250 cc. of wash water introduced at this time, it was not unusual to recover all 250 cc. Occasionally a few cubic centimeters was lost and, at other times, 2 or 3 cc. more was recovered. A series of experiments on the ability to recover known amounts of fluid by this method showed that the error averaged 2 per cent ($\pm$ 2 per cent).

At the close of the experiment the animal was killed, and a section of the colon was removed for microscopic examination.

In the experiments on the ileum, loops approximately equal in length to the colon were isolated near the terminal portion. The loops were cannulated with Paul tubes with attached fenestrated rubber tubes. Blood specimens were withdrawn from the large ileal vein opposite the selected loop.

The pancreatectomies were performed under sodium amytal anesthesia. The operations were done with aseptic technic, and the pancreas was removed with no injury to the duodenal vessels. A specimen of the blood sugar during fasting was taken before pancreatectomy, the morning following and each morning thereafter. When the blood sugar level during fasting indicated marked hyperglycemia, the absorption experiments were performed. Blood sugar levels prior to the dextrose absorption experiments varied from 225 to 325 mg. per hundred cubic centimeters. The interval between pancreatectomy and the dextrose absorption experiment varied from two to four days.

For the hypoglycemic animals, the following method was used. Specimens of blood from the peripheral and colic veins were taken, following which 10 units of insulin per kilogram of body weight was given subcutaneously. After a lapse of one-half hour, blood was again taken from the colic and femoral veins and the dextrose solution introduced, after which the absorption experiment was carried out in the usual manner.

All dextrose solutions were prepared from Bacto-dextrose. The dextrose in each instance was weighed and diluted to volume, after which the solution was titrated for the concentration of dextrose present. The latter figure is used throughout in the final calculations.

The effect on the blood sugar level of the introduction of an inert substance (paraffin oil) into the colon was observed in several experiments. These experiments were performed in the same manner as the usual absorption experiment, except that warmed paraffin oil was allowed to flow into the colon instead of the usual dextrose solution.

The effect of bacterial action and handling on a known amount of dextrose solution in a completely excised colon from a freshly killed animal was tested. The excised colon was washed and prepared in a manner similar to that used in the intact animal. Seventy-five ·cubic centimeters of an approximately 5 per cent dextrose solution containing 3.31 Gm. of dextrose was placed within the bowel, and the entire preparation placed in a beaker and incubated at 37.5 C. for two hours. At the end of that time the solution was recovered. The bowel and beaker were washed with 250 cc. of distilled water, and the dextrose content of each solution was determined.

All solutions recovered, as well as washings, were quantitatively analyzed by the Benedict method [37] immediately after completion of the experiment in order to eliminate the possibility of loss of dextrose through standing and bacterial action. Some of the solutions, especially when hypertonic dextrose was used, contained mucus, so that it was necessary to filter or centrifugate them before titration.

Because of the fact that the Benedict method is based on the reduction of copper, it was necessary to determine the possible presence of nondextrose copper-reducing substances in the solutions exposed to the intestinal mucous membrane. For this experiment the colon of an anesthetized animal was prepared in the usual manner, and 200 cc. of distilled water was introduced. After the lapse of two hours, the solution was withdrawn in the usual way and titrated by the Benedict method.[37]

37. Benedict, S. R.: The Detection and Estimation of Glucose in the Urine. J. A. M. A. **57**:1193 (Oct. 7) 1911.

All blood sugar determinations were made in duplicate by the Hagedorn and Jensen micromethod.[38] In several of the earlier experiments, Dr. Leon Jonas made simultaneous determinations by the Folin-Wu method. Except for the slightly lower level of the former determinations, the results were approximately the same.

RESULTS

The Absorption of a 5 Per Cent Dextrose Solution from the Ileum.— In tables 1 and 1a the results from three experiments are given. In every experiment water and dextrose were absorbed, and the concentration of the dextrose in the loop fell. There is a close relationship

TABLE 1.—*Five Per Cent Dextrose Solution in Ileum of Normal Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out, Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, in Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
815	11.2	240	4.1	214	3.6	—26	—10.4	9.84	7.70	0.41	8.11	1.73	82.4	17.6
1067	13.3	184	4.8	129	3.4	—55	—29.8	8.83	4.39	0.39	4.78	4.05	54.2	45.8
1068	7.8	158	4.5	138	3.95	—20	—12.6	7.11	5.45	0.35	5.80	1.31	81.6	18.4
Mean........		194		160		—34	—17.6	8.59			6.23	2.36	72.7	27.3

TABLE 1a.—*Peripheral and Ileal Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Ileum of Normal Dog*

Dog No.	Peripheral Venous Sugars, Mg. per 100 Cc.					Ileal Venous Sugars, Mg. per 100 Cc.	
	Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
815	83	85	86	88	90	85	97
1067	120	139	139	142	142		
1068	91	130	132	118	114	101	131

between the removal of water and absorption of dextrose, but dextrose apparently was absorbed more rapidly than water. The mean loss of fluid was 17.6 per cent, and the mean loss of dextrose, 27.3 per cent.

The peripheral venous sugars showed a tendency to rise. There is no correlation between the percentage of absorption of dextrose and the change in either the peripheral venous or the ileal blood sugars. In fact, of the two experiments in which ileal venous sugars were determined, the larger amount of dextrose absorption was associated with the smaller change in the ileal venous sugar.

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38. Hagedorn, H. C., and Jensen, B. N.: Biochem. Ztschr. **135**:46, 1923; **137**:92, 1923.

The Absorption of a 5 Per Cent Dextrose Solution from the Colon.— Eight experiments are tabulated in tables 2 and 2a. There is a striking difference in the mean loss of fluid in these experiments as compared to the ileal experiments. In only one of the eight experiments did the percentage of absorption of water exceed the minimum percentage of absorption in the first group.

Although the actual amount of dextrose introduced was greater in nearly every experiment, the mean percentage of absorption of dextrose

TABLE 2.—*Five Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out. Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, in Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
383	22.0	230	4.9	214	4.4	−16	− 6.9	11.27	9.42	0.60	10.02	1.25	88.9	11.1
652	17.3	230	4.5	220	4.0	−10	− 4.3	10.35	8.80	0.57	9.37	0.98	90.6	9.4
761	16.2	200	5.0	168	4.9	−32	−16.0	10.00	8.23	0.80	9.03	0.97	90.3	9.7
655	12.6	204	5.0	199	4.5	− 5	− 2.4	10.20	8.96	0.32	9.28	0.92	91.0	9.0
710	19.1	238	5.0	224	4.8	−14	− 5.9	11.90	10.75	0.27	11.02	0.88	92.6	7.4
834	10.6	190	4.7	184	4.5	− 6	− 3.1	8.93	8.28	0.21	8.49	0.44	95.1	4.9
942	15.9	155	5.0	141	5.0	−14	− 9.0	7.75	7.05	0.36	7.41	0.34	95.5	4.5
893	9.7	154	5.0	148	4.9	− 6	− 3.8	7.70	7.25	0.32	7.57	0.13	98.4	1.6
Mean........		200		197		−13	− 6.4	9.76			9.02	0.74	92.8	7.2

TABLE 2a.—*Peripheral and Colic Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
	Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
383	96	...	93	...	108	95	78
652	70	...	70	...	...	83	76
761	140	...	140	...	136	135	138
655	150	...	...	...	124	142	112
710	106	106	100	88	85	101	100
834	105	108	108	99	108	105	107
942	...	127	108	121	124	148	121
893	109	130	126	121	120	113	118

from the colon was decidedly less. There are, however, a slightly greater mean loss of dextrose than of water and a tendency for the concentration of the solution to fall slightly. Considered from the standpoint of actual loss of dextrose over a two hour period, however, the amount is indeed small, 90 per cent or more having been recovered after a two hour period.

In four animals the peripheral venous sugar changed very little. The changes that did occur were not always in the same direction. In

three experiments the initial blood sugar was high, a condition that is believed to be due to the excitation associated with the induction of anesthesia. The colic venous sugar was likewise high in these animals. There is no indication from the estimations of the colic venous sugar that dextrose was being absorbed rapidly.

Taken as a whole, the data do not support the hypothesis that any considerable amount of dextrose is absorbed in this type of experiment.

Histologic studies of the colon at the conclusion of the experiment showed a normal bowel.

TABLE 3.—*Seven Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out. Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, in Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
586	12.2	200	6.9	252	5.2	+52	+26.0	13.80	13.23	0.42	13.65	0.15	98.9	1.1
601	12.0	200	6.9	240	4.9	+40	+20.0	13.80	11.76	0.22	11.98	1.82	86.9	13.1
Mean........		200		246		+46	+23.0	13.80			12.81	0.98	92.9	7.1

TABLE 3a.—*Peripheral and Colic Venous Sugars Following Introduction of 7 Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
	Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
586	98	104	104	109	106	107	110
601	87	95	100	102	94	87	96

The Absorption of a 7 Per Cent Dextrose Solution from the Colon. —It was considered advisable to repeat the experiments on the colon, with hypertonic solutions of dextrose. In tables 3 and 3a are reported two experiments in which an approximately 7 per cent solution was used. At the end of the two hour period the amount of fluid in the large bowel was greater than that introduced. No definite conclusions can be drawn from the two experiments, but the range of dextrose absorption is within the limits of that obtained when a 5 per cent solution was used.

The peripheral and colic venous sugars tended to rise slightly, but there is a complete lack of correlation between the actual amount of dextrose lost and the changes in the peripheral blood sugar levels.

The histologic studies of the colon removed at the conclusion of the experiment showed only a slight increase in vascularity as evidenced by the greater number of filled capillaries.

The Absorption of a 10 Per Cent Dextrose Solution from the Colon.—In tables 4 and 4*a* are tabulated the results obtained from two experiments in which a more concentrated solution was used. As would be expected, the increase in the fluid content of the loop was even greater than when a 7 per cent solution was used. The concentration of dextrose was reduced, but this was largely due to the diluting effect

TABLE 4.—*Ten Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out, Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, in Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
20	11.8	158	9.7	214	6.0	+56	+35.4	15.33	12.84	0.55	13.39	1.94	87.4	12.6
410	17.0	250	9.7	339	6.2	+89	+35.6	24.25	21.02	0.55	21.57	2.68	89.0	11.0
Mean........		204		276		+72	+35.5	19.79			17.48	2.31	88.2	11.8

TABLE 4a.—*Peripheral and Colic Venous Sugars Following Introduction of 10 Per Cent Dextrose Solution in Colon of Normal Dog*

Dog No.	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
	Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
20	95	80	95	87	88	94	107
410	90	95	88	85	82	88	101

of the inflowing fluid. The mean amount of dextrose lost is slightly greater than that lost when a 5 per cent solution was used.

The peripheral venous sugar was lower at the conclusion of the experiment than at the beginning, while the colic venous sugar had increased in each experiment by 13 mg. per hundred cubic centimeters of blood.

The sections of the bowel removed at the conclusion of the experiment were similar to those removed from the previous group in that the only evidence of change was an increase in the number of filled capillaries.

The Absorption of a 5 Per Cent Dextrose Solution from the Colon of the Pancreatectomized Dog.—Five experiments are reported in tables 5 and 5*a*. The hyperglycemia in these animals was considerably greater

than that of the animals in group 2, who were excited during the induction of the anesthesia. The mean percentage of fluid absorbed was slightly greater than when a similar concentration of dextrose was placed in the colon of the normal dog. However, if the data from dog 387 are eliminated, the percentage of fluid absorbed is within the range of the normal animals. There is no evidence that dextrose is more rapidly absorbed under the conditions of this experiment. The percentage range of dextrose absorption in the five experiments is large,

TABLE 5.—*Five Per Cent Dextrose Solution in Colon of Pancreatectomized Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out. Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, in Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
387	9.8	144	3.75	110	3.3	—34	—23.6	5.40	3.63	0.83	4.46	0.94	82.6	17.4
390	9.9	232	4.7	220	4.7	—12	— 5.1	10.90	10.34	0.56	10.90	0.00	100.0	0.0
362	9.9	171	4.95	162	4.7	— 9	— 5.2	8.46	7.61	0.58	8.19	0.27	96.8	3.2
450	9.9	207	4.5	198	3.7	— 9	— 4.3	9.31	7.33	0.33	7.66	1.65	82.3	17.7
540	10.9	233	4.8	220	4.3	—13	— 5.5	11.18	9.46	0.72	10.18	1.00	91.1	8.9
Mean........		197		182		—15	— 9.3	9.05			8.28	0.77	90.6	9.4

TABLE 5a.—*Peripheral and Colic Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Colon of Pancreatectomized Dog*

Dog No.	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
	Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
387	278	261	276	265	260	250	290
390	315	299	311	299	...	303	268
362	225	196	175	220	...	244	261
450	325	310	315	298	284	263	295
540	258	253	271	279	271	252	261

but the mean dextrose absorption is approximately the same as in the previous experiments. Again there is a tendency toward a reduction in the concentration of the dextrose in the colon.

The peripheral and colic venous sugars show no consistent changes. There is a tendency for the peripheral venous sugar to decrease, but in dog 540 it increased. The colic venous sugars rose in four of the five experiments, and there appears to be some correlation between the percentage of absorption of dextrose and the rise in the colic venous sugar. In the one experiment in which a fall occurred in the colic venous sugar, there was no evidence of dextrose absorption.

The sections of the colon were entirely normal.

The Absorption of a 5 Per Cent Solution of Dextrose from the Colon of the Hypoglycemic Dog.—The results in two animals made hypoglycemic by the subcutaneous injection of 10 units of insulin per kilogram of body weight one-half hour before beginning the experiment are reported in tables 6 and 6a. The percentage of fluid absorbed is small indeed, the lowest for any group in which approximately isotonic solutions were used. The striking feature, however, is the

TABLE 6.—*Five Per Cent Dextrose Solution in Colon of Insulinized (Hypoglycemic) Dog*

Dog No.	Weight, Kg.	Solution Introduced, Cc.	Percentage Concentration In	Solution Out, Cc.	Percentage Concentration Out	Fluid Volume Change, Cc.	Percentage	Dextrose Introduced, Gm.	Dextrose Out, Gm.	Dextrose Recovered, in Washing, Gm.	Total Dextrose Out, Gm.	Dextrose Lost, Gm.	Percentage Dextrose Recovered	Percentage Dextrose Lost
161	16.6	240	5.2	228	4.2	—12	— 5.0	12.50	9.57	0.26	9.83	2.67	78.7	21.3
759	17.2	240	4.95	238	3.8	— 2	— 0.8	11.88	8.97	0.29	9.26	2.62	77.9	22.1
Mean........		240		233		— 7	— 2.9	12.19			9.54	2.64	78.3	21.7

TABLE 6a.—*Peripheral and Colic Venous Sugars Following Introduction of 5 Per Cent Dextrose Solution in Colon of Insulinized (Hypoglycemic) Dog*

Dog No.	Before Insulin	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
		Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	2 Hours
161	84	81	72	55	41	29	74	37
759	135	99	78	67	55	57	85	

relatively rapid absorption of dextrose, a mean of 21.7 per cent of that injected being lost in the two hour period. In these experiments dextrose was leaving the colon much more rapidly than was water.

The peripheral and colic venous sugars fell throughout each experiment so that, even though considerable dextrose was absorbed, the insulin was sufficient to prevent it from maintaining a constant sugar level. It must be considered, however, that the dose of insulin was unusually large. This dosage was used purposely in order to determine whether the rate of absorption from the colon could be increased under the conditions of a marked blood dextrose deficit.

The Effect of the Introduction of an Inert Substance (Paraffin Oil) into the Colon on Blood Sugar Levels.—Two experiments were per-

formed (table 7) in each of which paraffin oil similar in volume to the dextrose used in the earlier experiments was placed in the isolated colon. Specimens of blood were removed from the peripheral and colic veins. These showed slight variations. The colic venous sugars tended to go to lower levels at the end of the two hour period.

Bacterial Action.—The effect of bacterial action and handling on a known amount of dextrose solution in a completely excised colon, from a freshly killed animal, washed and prepared in a manner similar to the method used in the intact animal, was also tested. The 75 cc. of a 4.7 per cent solution of dextrose which was introduced contained 3.31 Gm. of dextrose. The bowel and its contents were placed in a beaker and incubated at 37.5 C. for two hours. At the end of that period, 70 cc. of the solution was recovered which contained 3.08 Gm. of dextrose. The washings contained an additional 0.14 Gm. of dextrose, bringing

TABLE 7.—*Peripheral and Colic Venous Sugars Following Introduction of Paraffin Oil in Colon of Normal Dog*

Dog No.	Weight, Kg.	Oil, Cc.	Peripheral Venous Sugars, Mg. per 100 Cc.					Colic Venous Sugars, Mg. per 100 Cc.	
			Start	½ Hour	1 Hour	1½ Hours	2 Hours	Start	End
1034	8.8	132	102	103	103	96	104	102	92
1046	7.7	154	113	115	114	122	112	106	101

the total amount recovered to 3.22 Gm. The dextrose lost through possible bacterial action and failure to recover was estimated at 2.6 per cent of the quantity introduced.

Determination of Nondextrose Copper-Reducing Substances in the Solutions Exposed to the Mucous Membrane of the Bowel.—Of the 210 cc. of tap water introduced into the colon of the living dog, but 150 cc. of fluid was recovered after the lapse of two hours. Titration was done by the Benedict method.[37] It was impossible to arrive at an end-point by using the entire 150 cc. recovered from the loop. Calculated at this point, the concentration of the reducing substances would be less than 0.03 per cent, and, from the color of the copper solution remaining, it would be safe to state that the amount was even lower than this. Even at the former level, the quantity is insignificant.

This experiment likewise demonstrates that tap water is readily and quickly taken up by the colon to the extent of 28.5 per cent in this one case.

Venous blood sugar determinations were made as well in this dog. The determinations of the peripheral and colic venous blood sugar showed little change.

It is evident from these experiments that there is a marked difference in the ability of the ileum and colon of the dog to absorb dextrose. In a two hour period, the normal anesthetized dog being used, the rate of absorption of dextrose from solutions varying from approximately 5 to 10 per cent was indeed small. The percentage of dextrose absorption is slightly greater than that given by McNealy and Willems [2] for 5 per cent solutions, but this may be due to the use of the large rectal ampulla. There appears to be a slightly greater absorption when 10 per cent solutions are used, but even here the actual amount absorbed was so small that even though the same rate could be maintained for a twenty-four hour period, the total dextrose absorbed would amount to only 27.7 Gm.

In two of the pancreatectomized animals the percentage absorption was considerable, but when calculated for the total amount absorbed, it is of little significance, a mean in all the pancreatectomized dogs of only 0.77 Gm. being absorbed over the two hour period.

It is interesting to note that, when a definite blood sugar deficit was maintained, as in the experiments on the hypoglycemic dogs, the percentage of absorption of dextrose was higher than in any of the colonic experiments and approximated the rate of absorption from the ileum. It would appear from these experiments that there may be some foundation in the observation of clinicians that diabetic persons in shock are improved by rectally administered dextrose. However, when time is an essential factor, it would not be wise to place the sole reliance on this method of administration of dextrose because the absorption is so slow.

The findings of McNealy and Willems [2] in regard to the rate of water removal when solutions of dextrose are placed in the large bowel have been confirmed. Tap water is absorbed much more rapidly. With the exception of one animal (dog 387, table 5), nothing approximating this rate of removal was observed in any of the experiments on the colon in which dextrose was used. Clinical experience has demonstrated that this is also true in man.

The blood sugar studies indicate that they are of little use as an indication of absorption where the rate of absorption is small. The findings in normal subjects presented in this paper are in essential agreement with those of Scott and Zweighaft.[3] There appears to be no direct correlation between the amount of dextrose absorbed and the peripheral blood sugar level. This may be due to the slow rate of absorption and to the stimulation of some mechanism which increases dextrose withdrawal from the blood stream. In the experiments in

which 7 and 10 per cent solutions of dextrose were placed in the colon, and in the pancreatectomized dogs, the colic venous sugars show some correlation with the amount of dextrose removed from the colon during the two hour period.

SUMMARY

Dextrose solutions are absorbed at a low rate when placed in the entire colon of the dog. Hypertonic solutions (10 per cent) are absorbed little faster than are isotonic solutions. When a marked dextrose deficit occurs in the blood, dextrose can be absorbed from the colon approximately as rapidly as it can be from a low ileal loop of the noninsulinized dog. The presence of dextrose in the solution in the colon, in the concentration used, causes a retardation in the rate of water absorption. The total amount of dextrose which can be administered and absorbed from the colon under the best conditions would appear to be too small for any considerable immediate therapeutic effect.

SELECTIVE STAINING OF DISEASED AREAS IN CARTILAGE BY INTRA-ARTICULAR INJECTION OF DYES

AN EXPERIMENTAL CADAVER STUDY, WITH SPECIAL REFERENCE TO ARTHROSCOPY

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The intra-articular injection of dyes is not a new procedure, though practiced only from the experimental standpoint to determine the absorptive capacity of the synovial membrane and the paths of absorption. A review of the literature indicates that no attention has been paid to the gross staining of cartilage by dyes. Tillmanns, in 1876, injected berlin blue into the bony canals of the amputated femurs of his experimental animals, after cutting away the bony plate that intervenes between the femur and the joint cavity. He intended to study the absorptive power of the synovia, without injuring either synovia or capsule. In seven cases, he noted a superficial staining of cartilage, easily washed out by a stream of water. Schreiber of Tübingen, in 1904, in analyzing the constituents of Belchier's madder, noted that purpurin, injected into the dorsal lymph sac of the frog, stained cartilage vitally a purple hue.

The gross staining reactions of cartilage in disease, as in jaundice and hematoporphyrinemia, are interesting. One deals here with pigments circulating in blood. Whether this is the case in ochronosis, which stains cartilage blackish, is still mooted. It is affirmed in all textbooks of pathology that in jaundice cartilage is not stained *intra vitam*. We have had several occasions to verify this. Schmorl has shown that the degenerated cartilage of intervertebral disks does take up the icteric stain *intra vitam*. It is the custom in the Pathologic Institute in Dresden to remove the entire right femur for examination. On the right side, then, in all cases of jaundice, the cartilage of the patella, of the femoral and tibial condyles and even of the menisci was stained green, the intensity of color varying with the length of exposure to air. When the left

or untouched knee joint was opened or was examined through the arthroscope, the cartilage and menisci were noted as definitely not stained.

This work was undertaken as a collateral study to arthroscopy,[1] following a suggestion of Professor Schmorl that it would be interesting to observe through the arthroscope the formation of arthritis experimentally produced by the use of colored irritants. I determined to test the general effect of a dye on the cartilage of cadavers recently deceased. I used the standard laboratory solutions of the various dyes used for tissue staining, diluted about 1 : 10 with water. The dye used was injected into the joint, usually the knee joint, and was immediately washed out by continuous irrigation. In many cases, the joint was then examined through the arthroscope to determine just what had happened in the interior of the joint. After a thorough examination, the findings were verified by opening the joint.

RESULTS

The following is a report of the work done.

Eosin.—Eosin apparently stains eroded areas on cartilage selectively and instantaneously; that is, normal or almost normal cartilage does not stain. The usual eroded areas on the under surface of the patella and on top of the intercondyloid notch stain particularly well. The stain is deep in the eroded areas but does not extend to bone. The greater the erosion, the deeper is the stain. Degenerated areas in cartilage, showing no particular erosion, stain from a light to a deep pink, though with not as great a selectivity as areas of erosion. Areas of "Wucherung" or overgrowth of new cartilage or fibrous tissue may stain better and deeper than small areas of erosion. Eosin, injected into a normal joint, will not stain cartilage. When the joint is opened and eosin is poured over the cartilage of the opened joint, all cartilage, whether normal, degenerated or eroded, stains almost uniformly. This may be due to exposure to air—the only explanation we can offer thus far for this phenomenon of paradoxical staining. Acid, such as hydrochloric acid, injected into the joint previous to the injection of the dye does not alter the staining powers of the dye.

Most of the joints into which eosin was injected were those of elderly people having arthritis of varying degree. Not only does cartilage stain, but it is seen that the synovial membrane, the crucial ligaments and the semilunar cartilages (menisci) also stain. The semilunar cartilages stain variously, best on their superior and inferior surfaces, but never in their depths. The staining is more pronounced if the

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1. Burman, M. S.: Arthroscopy or the Direct Visualization of Joints. An Experimental Cadaver Study, J. Bone & Joint Surg. **13**:669 (Oct.) 1931.

cartilage is degenerated, and if the inner free edge is irregular and fuzzy. The synovial membrane does not stain uniformly or deeply, but in scattered areas, sometimes more or less diffusely, not depending apparently on sites of degeneration. The infrapatellar fat pad has been noted to be stained through and through, indicating that there is a rapid diffusion of the dye through the synovia. Free synovial villi stain a delicate pink at times. The crucial ligaments, especially the anterior crucial ligament, stain only slightly. The color does not deepen on standing, when the opened joint is exposed to air.

The stain is always superficial and is present only in the upper cell layers of cartilage. Light scraping of the cartilage with a knife removes the stained areas easily and indicates the superficialness of the stain.

If hematoxylin is injected into the joint first and then eosin, after the hematoxylin has been washed out it is noted that the colors may mix or be separate, or that the pink of the eosin may overlie a clearly underlying blue of the hematoxylin. If, in the opened joint, hematoxylin is poured over a previously eosin-stained joint, one can see the blue of the hematoxylin overlying the pink of the eosin, with no tendency to fusion of colors. Each stain is separate. If in the opened knee joint, one half of the tibial condyles are stained with alcoholic eosin and one half with watery eosin, one notes that the resultant stains are uniform and identical.

Occasionally, when the dye is injected as from an inner puncture, the dye is noted to be confined to the inner half of the joint. This may be due to the fact that the joint is divided in halves by fat or adhesions that prevent the further spread of the dye.

Alcoholic eosin was injected into a knee joint in each of two adult rabbits. There was no staining of the cartilage, which was normal, though somewhat brownish, but a deep pink staining of the synovia and soft tissues took place. In one case, the menisci stained slightly. When the dye was poured over the opened joint, the cartilage stained relatively uniformly but not deeply. The menisci stained well.

Alcoholic and watery eosin stain cartilage alike.

Through the arthroscope, it is noted that the joint space is colored a fluorescent green, while the cartilage and soft tissues stain pink. Eroded areas are well seen. There is no metachromasia.

Eosin was injected into ten joints, alcoholic eosin into five and watery eosin into five. Eosin may be said to possess powers of selective staining, with particular predilection for eroded areas in cartilage and less for degenerated areas.

Hematoxylin.—Hematoxylin was injected into three or four joints. The staining of cartilage is slight, instantaneous and superficial, and not washable, uniform, metachromatic or selective, though degenerated areas

seemed to take the stain well. Staining is never widespread. In one case, the hematoxylin was injected into the knee joint of a deeply jaundiced man (carcinoma of the pancreas). The stain was slight, and, on exposure of the cartilage to air, after the joint was opened, the blue of the hematoxylin mixed itself with the yellow-green of the jaundiced cartilage, producing a weird color effect.

If hematoxylin is poured over the opened joint, it does not stain the cartilage uniformly, but a bit more diffusely than in the closed joint. The combination of eosin and hematoxylin has been already noted.

The semilunar cartilages stain on their superior and inferior surfaces, though not diffusely. The free edge may stain a bit more deeply. The synovial membrane and the crucial ligaments stain only slightly.

Acid hematoxylin (a brown solution) stains cartilage neither in the closed joint nor in the open joint.

Hematoxylin, as indicated in these few experiments, seems to be a weak dye, with no particular power of selectivity.

Methylene Blue.—Methylene blue was injected into five joints, the alcoholic solution into three and the watery one into two. Two of the joints showed absolutely normal cartilage. Staining of cartilage, with either the alcoholic or the watery solutions, is instantaneous, very diffuse, superficial, nonselective and not washed away by a strong stream of water, both in normal and in arthritic joints. Cartilage stains diffusely and deeply blue, without regard to the nature of the cartilage, though certain areas in cartilage do not stain at times. The synovial membrane and its villi are well stained. The menisci stain completely both on their two surfaces and on their free edge. The crucial ligaments stain particularly well. The quadriceps bursa stains a deep blue.

Metachromasia of soft tissues and of cartilage is definitely noted here, the color gamut being from blue to blue purple to red purple. This altered staining disappears on exposure to air.

In one case, only the inner half of the joint (an inner puncture being used) was stained, fat apparently blocking the spread of the dye to the outer half of the joint.

Pouring the dye over the opened joint does not increase the intensity of stain or alter its type or extent.

Alcoholic methylene blue was injected into a knee joint of each of two rabbits, with results identical to the foregoing ones.

Through the arthroscope, after the dye has been washed out, the stained areas are clearly visible. The joint space is a peculiar blue brown.

Sudan III.—This dye was used in two cases. Once, it was injected into the normal shoulder joint of a young man, with no staining of cartilage or synovia. In the second case, it was poured over the opened

knee joint of a man 34 years old, dead of tuberculosis; no immediate staining resulted. After a few minutes' exposure, fat was noted to be stained an orange yellow, and the fibrillar cartilage of the patella a slight yellow.

Alcoholic Methyl Violet.—This dye gave a strong, diffuse, blue-violet staining of all structures within the knee joint in the two cases in which it was used. Cartilage stains blue-violet, with possibly a slight predilection for degenerated areas. Synovia and its villi stain deeply blue. The semilunar cartilages stain diffusely well. The crucial ligaments stain well also. Metachromasia was noted in one case.

The stain deepens on exposure to air. If the dye is poured over the opened joint, the type or the extent of the staining is not changed. The staining of cartilage is superficial and instantaneous.

Lithium Carmine.—This dye, when injected into the knee joint (one case), stains instantaneously, very superficially and with an apparent predilection for diseased areas in cartilage, i.e., selectivity in staining. When it is poured over the opened knee joint, it does not stain cartilage further.

Neutral Red.—This dye was used in three knee joints. The stain is dark red, instantaneous, superficial and not washable; it is definitely selective for eroded areas in cartilage, and possibly less so for degenerative, fibrillar areas. Where the cartilage is fibrillar, the stain may then be diffuse. In one case, in an area of apparently normal cartilage, a deep staining took place; on cutting into the cartilage, a brown, degenerated area was observed beneath the surface. Possibly, then, this dye has the power to reveal early areas of degeneration in cartilage, not as yet visible to the eye. The menisci of the knee joint, the crucial ligaments and the synovia with its villi also stain a little.

When the dye is poured over the opened joint, one also notes that this dye has a definite predilection and selectivity for eroded and diseased areas in cartilage, though the staining here is a bit more diffuse.

A section of stained cartilage was examined by frozen section. It was noted that the stain was very superficial and confined to the upper cell layers, and stained the capsule, cells and intercellular substance equally well. The space between the capsule and cell, however, did not stain.

Bismarck Brown.—This dye was used in one case, giving a slight brown tinge to the cartilage. Poured over the cartilage of the opened joint, it did not stain.

Two Per Cent Gentian Violet.—This dye (used in one knee joint) stains irregularly, diffusely, instantaneously, superficially and without powers of selectivity. The staining is deep violet blue. All structures

stain almost equally well (cartilage, crucial ligaments, menisci, synovia). When the dye is poured over the opened joint, similar staining results. The staining capacities of the dye were examined through the arthroscope.

Concentrated Orange Solution.—The dye was injected into one hip joint with no resultant staining. The dye poured over the opened joint stained cartilage and synovial membrane slightly yellowish orange.

Toluidine Blue.—The dye was injected into one knee joint. Certain areas in cartilage, possibly degenerated, stained blue and also metachromatically. The stain is instantaneous, superficial, not washable and possibly selectively weak in staining. Menisci, crucial ligaments and the inner surface of the synovia stained a little. The metachromasia (blue to red purple) faded on opening the joint. The dye poured over the opened joint causes a slightly increased bluish staining of cartilage.

Concentrated Alcoholic Solution of Thionine.—When this dye is spilled over an opened joint, it stains cartilage and synovia very slightly, the stain deepening on standing.

Alum Carmine.—When this dye is injected into the closed knee joint, it does not stain; when it is poured over the opened joint, it stains cartilage and synovia slightly, superficially and unevenly.

Litmus Solution.—To test the action of indicators in their ability to stain joint cartilage, a watery solution of blue litmus (alkaline) was injected into the knee joint of one patient. It is to be noted that the water of Dresden is alkaline. No accurate chemical test of alkalinity was made. The color of the solution did not change, which indicates that the p_H of the joint fluid after death was still roughly alkaline. There was a slight bluish, superficial, easily washable staining of the joint cartilage. When litmus was poured over the opened joint, there was only a slight staining of cartilage, easily washed away by a stream of water. The color of the litmus did not change.

Bile.—A weak solution of bile was injected into the knee joint in one case with no resultant staining. No staining occurred when the bile was poured over the opened knee joint. The solution was evidently too weak to stain. It was noted that a drop of concentrated bile, poured accidentally from an opened gallbladder over the patella, stained it a green yellow, the stain being deep in color and not washed away by a stream of water.

<div align="center">COMMENT</div>

It can then safely be concluded that there are dyes that stain cartilage slightly or not at all, dyes that are diffuse in action, and dyes that are selective. The term "selectivity of action" means that these

dyes stain only eroded or degenerated areas in cartilage and leave normal cartilage unstained.

The course then is clear—to find those dyes that are selective and harmless. A series of experiments should be undertaken to determine the nature of dyes that stain selectively, the amount of dye necessary for use in a joint, the reaction of the joint to the dye, the absorption of the dye, the ability or inability of the dye to cause an experimental or clinical arthritis, the physical, chemical and biologic reasons that underlie selectivity, with special reference to the chemical nature of the dye and the biologic properties of the diseased area. Once this is determined by patient research, it will be possible to utilize these new facts in arthroscopy. Stained areas are clearly outlined through the arthroscope, much better than unstained areas, especially areas of erosion, which are difficult to visualize.

It is possible that the staining reactions described may not occur in living cartilage in the living person. The few animal experiments performed by me indicate this premise to be wrong. Whether one can call the intra-articular injection of dyes for the purpose of staining cartilage vital staining is questionable; it surely cannot be so called in the usually accepted sense of the term. What relation changes in the alkalinity of the synovial fluid bear to the staining of cartilage is not as yet known. Even after death, it appears that the synovial fluid, remains alkaline, and rarely in life does it reach a p_H lower than 7. It may be probable that the sometimes oily fluid exerts a protective effect against cartilage staining. Why there should be a difference between the staining powers of cartilage in the opened and in the closed joint is still conjectural. It is important to find a blue dye that stains selectively, since a red dye gives poor color contrast, especially in hyperemic or other inflammatory conditions of the joints.

CONCLUSION

Of the several dyes examined, eosin, neutral red and lithium carmine seem to stain diseased areas in cartilage selectively. This selective staining is of definite value in arthroscopy, delimiting, as it does, areas of disease in color, thus rendering visualization easy. The work presented here is only the most preliminary of studies.

FORTY-NINTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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This Report of Progress is based on a review of 195 articles selected from 359 articles dealing with orthopedic surgery appearing in the medical literature approximately between April 5 and July 30, 1932. A few selected articles of an earlier date are included. Only those papers that seemed to represent progress have been chosen for review.

CONGENITAL DEFORMITIES

Open Reduction of Congenital Dislocation of the Hip.—Howorth and Smith [1] reported observations in 72 cases of congenital dislocation of the hip in which the patients were treated by open operation from January, 1920, to July, 1929. In 26 cases the dislocation was bilateral. The average age was 4 years and 8 months. In the treatment of 46 of the 82 hips, previous attempts at closed reduction had failed.

The operations used were as follows: (1) simple reduction, 54 per cent; (2) gouging of the acetabulum followed by reduction, 20 per cent; (3) shelf operation, 11 per cent. In two hips it was necessary to reshape the femoral head. The anatomic and functional end-results were summarized; reduction was maintained in 66 per cent. Eighteen months after the first operations subluxation occurred in 31 per cent. Dislocation recurred in only 8 per cent. A good functional result was gained in 67 per cent.

1. Howorth, M. B., and Smith, H. W.: J. Bone & Joint Surg. 14:299, 1932.

Kidner[2] reviewed briefly the controversy between the schools advocating open and closed reduction of congenital dislocated hips. He has become convinced that open reduction gives the better result except in the rare young patient in whom the gentlest manipulation results in reduction.

He stated that the great obstacle to reduction, as shown on the operating table, was a redundant adherent capsule and not bony, cartilaginous or muscular changes as many workers had assumed. He found that little force was necessary usually to obtain reduction if the capsule was adequately freed. His operative approach consisted in an anterior incision extending downward from the anterior superior spine, retracting the sartorius medially and the tensor fascia and gluteus medius laterally. The capsule was reflected downward from the ilium as far as the superior border of the acetabulum. The capsule was then incised longitudinally, and the head of the femur was replaced in the acetabulum, which was enlarged if necessary. The redundant capsule was used as a reenforcing ligament. The leg was immobilized in abduction and internal rotation for from eight to twelve weeks. After physical therapy, walking was permitted. Kidner stated that inversion of the neck usually disappeared after reduction and in any case did not affect the end-result. He stated that in twenty-five cases in which operations were performed there was one postoperative death. In the others good results were obtained. There were no recurrences of the dislocation.

[ED. NOTE.—Open operation in congenital dislocation of the hip is coming into greater favor, particularly in the older or more difficult cases, because of the pathologic changes that often prevent reduction by manipulation. The end-results tabulated here, while on a small number of cases, are encouraging.]

DISTURBANCES IN BONE GROWTH

Osteitis Deformans.—Belden and Bernheim[3] made a study of 26 patients with osteitis deformans and as a result concluded that Paget's disease was a metabolic unbalance governed by the ductless glands. They believed that the apparent overaction of the parathyroid glands could best be controlled by a proper dietary and medical regimen. This was as follows: viosterol. 10 drops three times a day; tomato juice, 6 ounces (178 cc.) three times a day, and calcium lactate, 40 grains (2.6 Gm.) twice a day. Improvement was observed in all of the patients under this treatment.

2. Kidner, F. C.: South. M. J. **25**:350, 1932.

3. Belden, W. W., and Bernheim, A. R.: Radiology **18**:324, 1932.

Roentgenography of the Bones in Gaucher's Disease.—Reiss and Kato [4] studied 3 cases of Gaucher's disease in regard to the changes in the bones. The most constant and typical changes were observed in the lower end of the femur, which usually had a moth-eaten, punched-out appearance. There was an osteoporosis throughout the shaft. Pathologic fracture without bony displacement was common. The other long bones were frequently involved. Compression of the vertebrae was observed without a disappearance of the intervertebral disk, although the disks might be invaded extensively by the disease.

The Growth of Bone.—Jansen,[5] in the Lady Jones Memorial Lecture delivered at Liverpool on Feb. 17, 1931, traced the development of certain concepts in regard to the formation and growth of bone. He showed how both excessive and subnormal functional pressure led to the absorption of lime salts from bone, and that an enhanced deposition of lime salts occurred somewhere between these two extremes. He believed that in exercise the bones were as well developed as the muscles. Two aspects of the increased vulnerability of the rapidly growing cells of bone were given: (1) Injurious agents of all kinds might cause feebleness of growth. (2) The signs of feebleness of growth were given in three degrees: (*a*) The slight degree was characterized only by muscular weakness, weak feet, a prominent abdomen, round shoulders and blue hands and feet; there was usually an overgrowth in adolescence. (*b*) The moderate degree was represented by the knock-kneed child, neither too tall nor too short. (*c*) The severe degree was characterized by severe muscular weakness; all of the cartilages of growth were affected, and the entire skeleton lagged behind the normal in growth. The severe form of enfeeblement of growth was observed in the first few years of life. Enfeebled bone substance showed two characteristics: increased fatigability and increased irritability. By studying the quantitative changes in growth in the locomotor apparatus, evidence of a feeble constitution might be obtained. The discovery and removal of the causes of such enfeeblement of growth would remove much disease and crippling of the human race.

[ED. NOTE.—Jansen's views on the various factors influencing the growth of bone are thought provoking and merit consideration and for this reason they are worth while even if we are unable to agree with all of his conclusions.]

NEOPLASMS

Fibrosarcoma of Bone.—Geschickter [6] stated that the osteogenic portions of the bone do not give rise to sarcoma of the true spindle cell

4. Reiss, O., and Kato, K.: Gaucher's Disease: Clinical Study, with Special Reference to Roentgenography of Bones, Am. J. Dis. Child. 43:365 (Feb.) 1932.

5. Jansen, M.: Surg., Gynec. & Obst. 54:175, 1932.

6. Geschickter, C. F.: So-Called Fibrosarcoma of Bone: Bone Involvement by Sarcoma of the Neighboring Soft Parts, Arch. Surg. 24:231 (Feb.) 1932.

type. Connective tissue tumors in bone arise from fibroblasts with a tendency to bone formation or from precartilaginous connective tissue destined to form bone via the intracartilaginous route. His study of thirty-one cases showed that the histologic composition of the new growth was a more reliable index of its clinical and pathologic behavior than its anatomic location or apparent relationship to bone. Fibrospindle cell tumors should be studied in regard to the transition from oat cell to spindle cell to fibrospindle cell to adult fibroblasts. The more primitive the connective tissue cell, the more malignant was the tumor. In the undifferentiated oat cell type, neither excision nor roentgen therapy offered more than temporary relief. In neurogenic tumors involving bone, a similar microscopic gradation could be made. The more malignant the tumor, the greater was the number of large pleomorphic nuclei and the more closely packed the spindle cells. The prognosis was extremely bad, death usually occurring in two years. The author mentioned that bone was sometimes invaded by connective tissue tumors arising from outside the bone which gave a similar clinical picture, such as angiomas, myosarcomas and lipomas. When the fibrosarcoma was not of the oat cell type, an attempt to eradicate the disease locally was justifiable. In the oat cell type, immediate amputation was indicated. Amputation was the treatment of choice in neurogenic sarcoma involving the bone. For angiomas, local excision followed by irradiation seemed the best treatment. Local excision was advocated for lipomas and amputation for myosarcomas.

THE BACK

Backache; Anatomic Consideration.—Willis [7] reported his studies on the anatomy of many spinal columns at Western Reserve University. He was particularly interested in the anomalous developments, such as spina bifida occulta, asymmetric sacralization and the "separate neural arch," a defect in one or both laminae occurring between the superior and inferior articular processes of the lumbar vertebrae, most often the latter. The relationship of this last anomaly to spondylolisthesis was, as pointed out by the author, well known. Willis found the defect present in 79 instances in a study of 1,520 skeletons, an incidence of 5.9 per cent.

Spondylolisthesis.—Meyerding [8] reviewed the findings in 207 cases of spondylolisthesis; 148 were in male patients and 59 in female patients. The condition was found to be due to instability of the lumbosacral articulation and to congenital defects in the lumbosacral region. A number of patients had spondylolisthesis without symptoms. The

7. Willis, T. A.:   J. Bone & Joint Surg. **14**:267, 1932.

8. Meyerding. H. W.:   Surg., Gynec. & Obst. **54**:371. 1932.

chief symptom was backache, with or without radiating pain. Prominence of the sacrum and a shortened torso were commonly observed. Neurologic disturbances were rare. X-ray pictures, particularly lateral ones, helped greatly in the diagnosis. While spinal support often relieved the symptoms, the author advised fusion of the sacrum to the lower lumbar spine.

Typhoid Spine.—Wang and Miltner[9] reported 2 cases of typhoid spine, 1 of which also presented a destructive arthritis of the sacro-iliac joint. There was complete recovery in both cases, with bony ankylosis of the spines in the involved areas. The treatment used was prolonged recumbency followed by a spinal support. There was bacteriologic verification of the diagnosis in both cases.

Gibbus Resulting from Tetanus.—Ciaccia[10] collected cases from the literature, and added 2 of his own in which gibbus developed following tetanus. All of the lesions were dorsal in location excepting 2 in the lumbar region. They were characterized by an absence of destruction of the intervertebral disks, an absence of abscess formation and partial collapse of from one to three vertebral bodies. Various etiologic factors were discussed at length; chief among these was the spontaneous vertebral collapse in the presence of maintained muscular spasm. In 1 case Ciaccia fused the spine, and in the other he obtained a satisfactory result by conservative therapy.

SUPPURATIVE ARTHRITIS

Suppurative Arthritis of the Hip.—From a study of 18 septic hips in 17 children, Caldwell[11] concluded that it was important to establish the diagnosis of such a condition early and to determine, if possible, whether the infection was primarily an osteomyelitis of the femoral neck or whether it originated from the synovial lining of the joint. In all of the 17 cases the infection was of hematogenic origin. To wait for roentgen evidence in the presence of sepsis was often disastrous, because this rarely occurred before two weeks had elapsed. He favored early aspiration of the joint as a means of establishing the diagnosis. Twelve hips were drained by anterior incisions, 2 posteriorly and 4 by incisions over the inner side of the thigh, where abscesses were pointing. Postoperative traction in abduction was considered most essential to prevent dislocation. In cases in which there was a primary osteomyelitis or epiphysitis, ankylosis of the joint was apt to result. Frequent x-ray pictures during convalescent treatment were desirable to determine whether there was osseous involvement.

9. Wang, L. K., and Miltner, L. J.: Chinese M. J. **46**:1, 1932.

10. Ciaccia, S.: Chir. d. org. di movimento **16**:531, 1931.

11. Caldwell, G. A.: Acute Suppurative Conditions of the Hip Joint, J. A. M. A. **98**:37 (Jan. 2) 1932.

TUBERCULOSIS

Operative Treatment of Tuberculosis of the Joints.—Henderson [12] reviewed the present trends in the treatment of tuberculosis of the bones and joints. He stated that conservative treatment has its greatest field of usefulness in children, while operative treatment aiming to ankylose the diseased joints and to eradicate the disease is the treatment of choice in adults. It is important to select the patients for operation carefully, since the results in America are still poor, owing in large part to the unwillingness of patients to continue treatment sufficiently long. Each patient must be studied before the type of treatment can be decided. In general, patients in whom operative treatment is advisable should be beyond the age of puberty, free from active pulmonary tuberculosis and from tuberculosis of the genito-urinary tract and also in good general health. The author advised against extensive operative procedures in the presence of draining sinuses. In a series of more than 600 cases, the operative mortality was less than 1 per cent.

Liver Meal in the Treatment of Amyloidosis in Surgical Tuberculosis.—Whitbeck [13] treated 7 patients with amyloid disease following tuberculosis of the bones and joints with liver extract. Powdered whole liver was used and given in doses of 1 drachm (3.9 Gm.) three times daily. Two patients died, 1 from an intercurrent infection and the other from cardiac failure. The other 5 showed benefit three months after therapy had been instituted, and thirteen months later there was distinct improvement, as evidenced by a diminution in the size of the liver and spleen, less anemia, less ascites and improvement in the general state of nutrition. However, in each case the Congo red test was positive at the end of eighteen months, indicating that sufficient lardaceous material was present in the organs to absorb the dye and to remove it completely from the blood.

POLIOMYELITIS

Production of Antiviral Substances.—Howitt,[14] by the injection of poliomyelitis virus into 2 sheep and a goat over a period of years, was able to produce antiviral substances capable of protecting monkeys against infection. The author demonstrated also by a higher percentage of recoveries that the intramuscular route was preferable to the combined intravenous and intrathecal routes in giving convalescent serum to monkeys in the preparalytic stage of poliomyelitis.

Convalescent Serum in Preparalytic Poliomyelitis.—In a fairly well controlled group of patients in the preparalytic stage of poliomyelitis in

12. Henderson, M. S.: Minnesota Med. **15**:141, 1932.

13. Whitbeck, B. H.: J. Bone & Joint Surg. **14**:85, 1932.

14. Howitt, B. F.: Proc. Soc. Exper. Biol. & Med. **29**:118, 1931.

southern New England in 1931, Kramer and his co-workers [15] made a careful study of the therapeutic effect of human convalescent poliomyelitic serum given by the combined intraspinous and intravenous routes. The authors were unable to obtain conclusive evidence that the convalescent serum was of value, or, on the other hand, that it was valueless.

Abortive Poliomyelitis.—Paul and his associates [16] reported the results of an epidemiologic study of poliomyelitis with particular reference to cases of "abortive" poliomyelitis. By "abortive" poliomyelitis was meant a minor illness showing more or less regular characteristics and occurring during an epidemic of poliomyelitis. The symptomatology of these minor illnesses was not specific, but was essentially that of an acute infection of short duration, symptoms of fever, sore throat, headache and vomiting dominating the picture. A survey of 222 families, in each of which 1 or more cases of poliomyelitis developed, showed that in from 32 to 39 per cent of the other children, i. e., those not coming down with poliomyelitis, minor illness developed coincidentally with the onset of the known cases. In 60 control families studied, it was found that only 9 per cent of the children had minor illnesses during the time of the epidemic. It seemed reasonable to suppose that at least some of the minor illnesses were related to orthodox poliomyelitis. Only if it could be shown that a child became immune subsequent to the development of a minor illness could it be assumed that he had passed through an attack of the disease. This proof awaited further knowledge of the nature of immunity and of the means of measuring it.

Poliomyelitis in California.—Meals and Bower [17] reviewed the 1930 epidemic of poliomyelitis in southern California; 350 cases were studied. Spread by "healthy carriers" was frequently observed. The patients were seen, on the average, on the fourth day of the illness. In 11.7 per cent of the cases, paralysis was found on the first examination. In 12.86 per cent, the spinal fluids were negative, but the patients showed characteristic neurologic findings. Twenty-two per cent were negative neurologically, but showed the usual changes in the spinal fluid. Treatment was almost wholly with pooled convalescent serum plus rest and immobilization, with dietetic and eliminative measures. Serum was given, either 15 cc. intrathecally or 30 cc. intramuscularly or intravenously; the mode of administration depended on the severity and the advancement of the disease. The authors preferred the intravenous

15. Kramer, S. D.; Aycock, W. L.; Solomon, C. I., and Thenebe, C. L.: New England J. Med. **206**:432, 1932.

16. Paul, J. R.; Salinger, R., and Trask, J. D.: "Abortive" Poliomyelitis. J. A. M. A. **98**:2262 (June 25) 1932.

17. Meals, R. W., and Bower, A. G.: J. Lab. & Clin. Med. **17**:409, 1932.

or intramuscular administration of serum when there were no phenomena of the central nervous system. In 82 per cent of the cases, the fever abated and the subjective symptoms subsided after the intra-cisternal injection of serum. In this series there were 60.9 per cent complete recoveries. In 25.66 per cent there was mild residual paralysis, and 10.28 per cent showed more extensive paralyses. The mortality was 3.16 per cent. In the entire country the death rate during this epidemic was 7 per cent.

[ED. NOTE.—The therapeutic effect of convalescent serum in the treatment of preparalytic poliomyelitis is still sub judice. The most carefully controlled observations, although small in number, throw a doubt on the usefulness of the serum. Its use, however, should be encouraged until the matter is settled.]

ARTHRITIS

Hemophilic Arthritis.—Key [18] reported a thorough study of a case of chronic hemophilic arthritis of the knee in which the patient was operated on because of a mistaken diagnosis. Macroscopic and micro-scopic studies were reported. Key divided hemophilic joints into two types: the acute hemarthrosis and the chronic arthritis. The first type represented the first or early attacks in which the picture was one of intrasynovial hemorrhage, varying in the severity of the symptoms according to the amount of hemorrhage. The second type, a joint into which there had been numerous hemorrhages over a period of years, showed a rather characteristic group of signs and symptoms. Grossly and clinically, this joint simulated almost any of the various types of chronic arthritic lesions. When the lesion was opened, the appearance was characteristic—a thickened, deeply pigmented synovial membrane with a fibrous subsynovial tissue, maplike destruction of the articular cartilage, replaced by either fibrous tissue or unorganized blood clot, and atrophic irregular subchondral osseous structure. A flexion deformity of the joint was frequently seen. Operative intervention was contraindicated; conservative therapy alone should be used. An excellent study of the various types of joints was given, as well as a review of the scant literature on these lesions.

Syphilitic Arthritis with Effusion.—Among 112 cases of acute and chronic arthritis with effusion, Kling [19] found that 9 (8.1 per cent) were due to syphilis. All cases showed late manifestations of the disease. Over half of the cases were due to congenital syphilis. Seven showed involvement of the synovial membrane only; 1 patient had a juxta-articular gumma; another had osteochondritis and periostitis.

18. Key, J. A.: Ann. Surg. **95**:198, 1932.
19. Kling, D. H.: Am. J. M. Sc. **183**:538, 1932.

Kling based the diagnosis on (1) the presence of syphilis as shown by the Wassermann reaction of the blood and by other syphilitic lesions, i. e., keratitis and gumma, and (2) examination of the affected joint. He found that complete examination of the fluid of the joint was most important, particularly the Wassermann reaction. He found that a therapeutic test was of value in doubtful cases, always proving of benefit if the diagnosis was correct.

CIRCULATORY DISTURBANCES

Raynaud's Disease.—Allen and Brown [20] studied 150 cases of Raynaud's disease in order to determine the minimal requisites for diagnosis. They found that the symptoms described by Raynaud were necessary for a diagnosis. These were: gangrene or trophic disturbances limited almost wholly to the skin, symmetrical or bilateral involvement, absence of evidence of any occlusive lesions of the peripheral arteries and intermittent attacks.

Deep Ligation of the Vein for Gangrene.—Pearse [21] reported the results of deep ligation of the vein in 20 cases of diabetic and arteriosclerotic gangrene. Thirty-one additional cases from the literature were reviewed. Ligation of the external iliac vein, the femoral vein or the popliteal vein was done. Of 20 patients so treated, the results in 8 were successful, the results in 8 were failures, and 4 patients died within a year without amputation. The cases were divided into 3 classes: (1) cases in which amputation of the leg should be done; (2) those in which amputation should not be done, and (3) borderline cases. The beneficial results from ligation of the vein were warmth, diminution of pain and objective changes in the limb. Edema rarely occurred. Additional factors in the treatment of such limbs were enumerated in a discussion of the preoperative and the postoperative treatment.

20. Allen, E. V., and Brown, G. E.: Am. J. M. Sc. **183**:187, 1932.

21. Pearse, H. E.: The Use of Vein Ligation in the Treatment of Arteriosclerotic and Diabetic Gangrene, J. A. M. A. **98**:866 (March 12) 1932.

(To be Concluded)

ACUTE OSTEOMYELITIS OF THE VERTEBRAE

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Acute osteomyelitis of the vertebrae constitutes a clinical entity of interest and importance to both the internist and the surgeon. The disease consists of an acute suppurative spondylitis generally consequent on metastatic infection of the vertebrae at the time of a previous bacteremia, occasionally the result of the involvement of the vertebrae by a local inflammation that has spread by direct extension. The malady is serious, is often not recognized promptly and is attended with a considerable mortality. The American literature has paid this subject scant attention. The following sixteen cases, proved by operation or necropsy, have occurred in the Mount Sinai Hospital chiefly during the past seven years and are presented to serve as a basis for the analysis of the disease and its clinical aspects. The aim of this study is clinical. For statistical and theoretical discussions of the subject, the reader is referred to Volkman,[1] Wilensky [2] and Borchers.[3]

CLINICAL CONSIDERATIONS

In general, the history, mode of onset and generic symptomatology of all the cases had many features in common. However, for clinical purposes, it has been possible to subdivide the series into four groups according to the nature of the presenting clinical condition. The latter was usually a complication, e. g., epidural abscess, and often dominated the clinical scene.

History.—It is most important to elicit the history of a preexisting lesion which may have been the focus for a bacteremia. In contrast to osteomyelitis of the long bones, to which the young are so prone and which is so often cryptogenetic, the presumable portals of entry were established in fifteen of the sixteen cases. These included boils and carbuncles, previous chronic osteomyelitis, pneumonia, cellulitis of the

1. Volkman, J.: Ueber die primäre akute und subakute Osteomyelitis purulenta der Wirbel, Deutsche Ztschr. f. Chir. **132**:445 (Jan.) 1915.

2. Wilensky, A. O.: Osteomyelitis of Vertebrae, Ann. Surg. **89**:561 (April) 1929; 731 (May) 1929.

3. Borchers, G.: Ueber die primäre akute und subakute Osteomyelitis purulenta der Wirbel, Arch. f. klin. Chir. **158**:168 (Feb.) 1930.

arm, phlebitis of the hepatic vein radicles subsequent to cholangeitic abscess of the liver, acute bacterial endocarditis of the aortic and mitral valves, cystitis with purulent prostatitis, mastoiditis with mastoidectomy, lateral sinus thrombosis, purulent bronchitis in cachexia (phlebitis of the smaller radicles of the pulmonary vein?) and a secondarily infected hematoma. Typhoid fever, paronychia, alveolar abscess, pharyngitis and mastitis may also be sources of bacteremia with metastatic osteomyelitis.[1] A history of true rigor may be obtained, and is of great significance even though it may have occurred many months before. Trauma played no appreciable rôle in this series of cases.

Mode of Onset.—As well as could be determined, the shortest time in which objective evidence of a local pathologic process developed was ten days (case 2). In all the other cases, at least two weeks were necessary. Generally, a little local pain or rigidity was complained of; this gradually became more severe until there was complementary evidence of local disease. In no case was there sudden onset with severe local symptoms and signs pointing to the underlying processes. *Pari passu* with the aggravation of the local condition was the intensification of the systemic indications of the infection.

Generic Characteristics.—In contrast to the osteomyelitis of the long bones, only two of these cases occurred in children. The patients were all febrile and apparently suffering from an infection, with the customary manifestations of fever, tachycardia, leukocytosis, albuminuria, etc. These observations show the necessity for careful investigation when the process is not superficial and therefore obvious. None of the cases presented the appearance of rapidly fatal overwhelming infection, with signs only of generalized intoxication without localization, which is occasionally seen in osteomyelitis of the long bones. The difference may be due to the relatively small amount of marrow infected, in contrast to the amount involved in disease of the long bones.

The following local characteristics may be common to osteomyelitis of the spine, no matter where situated:

1. There is pain, especially on motion. The aggravation of the pain on motion may be due to the spasm of the contiguous musculature or to pressure on a diseased intervertebral disk. Pain on jolting is often absent and is less prominent than in tuberculous spondylitis.[1]

2. Local tenderness may or may not be present over the spinous processes. It is less apt to be present when only the bodies of the vertebrae are diseased. In two cases pain was maximal over normal vertebrae. In case 10, clinically, tenderness had been elicited over the spinous processes of the second and third sacral vertebrae; however, at necropsy, the osteomyelitic foci were found in the second and third lumbar vertebrae.

3. Signs of local inflammation generally indicate perforation and are most commonly present when the laminae or processes are affected, but may be present in exclusive involvement of the vertebral bodies.

4. There is a grating sensation on palpation, owing to sequestration of a spinous process.[1]

5. Local deformity with actual gibbus may occur, owing to the collapse of the diseased vertebrae, as in case 13. Generally, there is only transient deformity, due perhaps to muscle spasm which disappears with the subsidence of inflammation.[1]

The cases may be divided into the following groups:

Group I. The most frequent clinical picture presented is that of abscess formation. This may occur anywhere along the spine. Although the pathologic process is everywhere essentially the same, the difference in the location of the site involved causes a variety of clinical pictures. In the order of frequency these are as follows:

A. The abscess generally presents in the back, near the vertebral column. The skin over the suppurating area most often reveals no local etiologic lesion (when the process is metastatic in origin). There may be no signs or symptoms of underlying bony disease. In this series, ten days was the shortest period of time for the formation of an abscess large enough to be recognized. At operation bare bone is felt at the base of the abscess cavity. This establishes the osteomyelitic origin of the abscess.

B. The next most frequent situation for the abscess is the region of the psoas magnus muscle. A tremendous collection of pus may be present here and yet not cause a swelling conspicuous enough to be detected by careful physical examination. Its existence may have to be inferred from the presence of tender enlarged inguinal lymph nodes associated with homolateral psoas spasm. When a tuberculous abscess of the spine gravitates along the psoas muscle down to the inguinal region, caseating inguinal adenopathy occasionally develops in a similar fashion, but the swelling created is cold, indolent and generally not tender. Because of the involvement of lumbar nerve roots by the inflammatory process, there may be abdominal distention, pain and rigidity, so that one may be inclined to infer the existence of an acute surgical inflammation within the peritoneal cavity ("acute abdomen"). The presence of costovertebral tenderness, with a local mass or spasm of the lumbar muscles and purulent urine, may lead to the erroneous diagnosis of perinephritic abscess, secondary to a perforated cortical abscess of the kidney. Since this is frequently a concomitant metastatic lesion, the diagnosis may be established with certainty only at operation.

C. An apparently idiopathic abscess may present in the buttock. At operation bare bone may not be felt at the base of the abscess

cavity. In such a case one must investigate the lumbar and sacral vertebrae for the presence of an osteomyelitic focus. A collection of pus arising from these vertebrae may gravitate down along the tissue planes, pass through the major sciatic foramen and present in the buttock. It may also pass over the crest of the ilium and present in the buttock. It is because of this devious route that bare bone is not encountered at operation. The collection of pus may pass through the minor sciatic foramen and present beside the anus. This may be the explanation for a persistently draining ischiorectal abscess.

D. The mediastinum may also be the seat of abscess formation. The patient may complain of pain in the chest or abdomen, a pleuritic friction rub may be heard, and later there may be present an area of dulness with diminution of breath sounds. Constant dry cough and hiccup may occur. The diagnosis of mediastinal abscess is made by (1) a history of a focus capable of giving rise to a bacteremia, (2) localized tenderness over the spinous processes of the thoracic vertebrae and (3) roentgenographic evidence of widening of the mediastinum, like that produced by mediastinal collections of fluid.

Group II. The second most frequent clinical group is that in which the patients present a variety of complaints referable to the nervous system. There may be paresis or paralysis of a limb, sphincteric disturbances, abnormalities in the reflexes, impairment of sensory perception or tenderness along the peripheral nerves. Because of the presence of an infection elsewhere in the body and findings that simulate those of myelitis or peripheral neuritis, an erroneous diagnosis of "toxic myelitis" or "toxic neuritis" is often made. The signs and symptoms are generally due to involvement of the nerve roots by the inflammatory exudate or to compression of the spinal cord, which is consequent on pachymeningitis, epidural abscess, etc., the result of perforation of the osteomyelitic focus. The latter must be suspected when a patient with a history of an inflammatory focus capable of giving rise to a bacteremia shows signs and symptoms referable to disease of the spinal cord. Of great diagnostic value are tenderness over the spinous processes, signs of a level lesion, evidences of spinal subarachnoid block and pleocytosis in the cerebrospinal fluid. This group of related conditions in a patient suffering from an infection is most suggestive of perforation of an osteomyelitis of the vertebrae.

Group III. In this group may be classed those patients who present only pain in the back and fever. No other findings may be elicited despite elaborate efforts to determine the cause of the pain. Symptomatic measures fail to give relief. Roentgenographic examination of the painful segments of the spine may yield negative results despite months of suppuration. Diagnosis is most difficult in these cases and may be established only by operation. When the general clinical picture

indicates the existence of infection and there is a history of previous bacteremia, an exploratory operation may have to be performed, especially when the painful area is tender. It may be fatal to postpone operation until one has the confirmatory evidence of a complication (spinal meningitis).

Group IV. The fourth group includes those patients who suffer from widespread suppuration consequent on a bacteremia. There are multiple abscesses throughout the viscera, e. g., in the kidneys, spleen and lungs, and, coincidentally, abscesses in the vertebrae. The clinical picture produced is a summation of the signs and symptoms due to the suppurative spondylitis, as described in the first three groups, and those dependent on the nature and location of the coincident metastatic abscesses elsewhere and the complications subsequent to them.

The cases comprising this group are least in importance from a therapeutic standpoint. Even if the bone focus is susceptible to adequate treatment, death occurs because of the already established, generalized, metastatic abscesses. However, in cases in which the osteomyelitic focus is itself the source of a bacteremia, often persistent, adequate local treatment may eradicate the focus and terminate the bacteremia; the metastatic foci may heal completely, and the patient may then recover.

PATHOGENESIS

There are two ways in which the vertebral infection may occur. Most frequently, there is a localized infection which gives rise to a bacteremia; bacteria localize in the vertebrae and cause an osteomyelitis. This mode of development is well illustrated by case 10, in which a pneumococcus type I was recovered from the pus in the infected mastoid process, from the blood stream on the day after operation and from the pus in the mediastinal abscess produced by the vertebral osteomyelitis. This development can be traced in cases 5, 10, 11 and 14. In rare ·instances there is a local inflammation which spreads and involves the vertebrae by direct extension (case 6).

BACTERIOLOGY

In the literature the following have been described as causative organisms: Staphylococcus aureus and albus, Streptococcus pyogenes. Bacillus typhosus, Micrococcus tetragenus,[1] B. paratyphosus A[4] and B. perfringens.[5] In addition to these there were found in this series Streptococcus viridans, the pneumococcus, types I, III and IV. and the Friedländer bacillus. In view of the variety of organisms that have

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4. Zanboni, G.: Osteomyelite degli archi vertebrali della II-III-IV lombare da paratifo A, Ann. ital. di chir. 5:499 (May) 1926.

5. Laborde, J. P. A. M.: Étude sur les spondylites staphylococciques de l'adulte. Thèse. Paris. 1926, vol. 39. no. 93.

already been found responsible, it would not be wise to rule out the diagnosis if there should be isolated from a patient suspected of vertebral osteomyelitis an organism (e. g., B. coli) that has hitherto not been described in this condition (see addendum).

In six of the cases, blood cultures were taken, and in each case bacteria were recovered from the blood stream. In four of the cases, the focus causing the bacteremia was distant from the local bone disease, e. g., hepatic vein phlebitis; in one (case 6), it was the local inflammation, and in one other (case 12), it was a phlebitis, complicating a perforation into the soft tissues of the vertebral suppuration. Depending on the nature of the causative focus, the bacteremia was transient (cases 6 and 10) or lasted until the death of the patient (cases 11, 13, 14 and 15).

PATHOLOGY

Anatomically, the cases can be divided into two groups, depending on whether the bodies or the processes of the vertebrae are the sites of the inflammation. In ten cases the bodies were involved; in eight of these there was frank suppuration, often with abscess formation; in one (case 10), the body was merely denuded of periosteum, roughened and tender, and in one other the nature of the corporeal involvement could not be determined. In only three cases was a bony process found to be the seat of the inflammation. In three cases it was not possible to ascertain definitely which portion of the vertebrae was diseased. In the cases in which the process was involved, the inflammation was chiefly superficial, the exposed bone being merely bare and rough. Perforation was earlier when the inflammation occurred in a process, perhaps because of the smaller volume of bone affected.

It is customary to divide vertebral osteomyelitis into cortical, or subperiosteal, and medullary types. To the former belong the cases that present only superficial infection of the bone, which is denuded of periosteum, rough and tender; they occur chiefly in infection of the processes. To the latter belong the cases with frank suppuration and abscess formation; they occur chiefly in infection of the vertebral bodies. If the necrosis is sufficiently extensive, the body may be crushed.

Worthy of mention is a chronic form of the disease described by Radt.[6] In this condition the process may last for many years, with the formation of an ossifying perivertebral granulation tissue which compresses the nerve roots and produces severe, intractable radicular pains.

In cases of bacteremia, it is probable that organisms are carried to many bones besides those which become diseased. Just why certain vertebrae fall a prey to the bacterial invasion is impossible to state. In one case two widely separated vertebrae were infected, while in four

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6. Radt, P.: Ueber. chronische Osteomyelitis der Wirbelsäule und des Kreuzbeins, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **41**:389 (May) 1929.

cases two annectent vertebrae were diseased. In only two cases can there be implicated a contributory factor, favoring the development of the metastatic process. In one (case 15) there was an old local spondylitis, and in the other (case 16) Hodgkin's infiltrations were present in the vertebral body.

When perforation occurs posteriorly, a superficial abscess forms; it is readily drained, and convalescence is generally uneventful.

Serious complications are usually consequent on perforations that do not come from the processes or laminae and that are not directed posteriorly. Irrespective of the situation of the disease process, the most frequent and most serious complication is that of involvement of the central nervous system. Compression of the spinal cord may be caused by: (a) an epidural abscess, secondary to perforation into the epidural space; (b) a subdural abscess secondary to epidural infection; secondary to the subdural infection, spinal leptomeningitis may occur and spread to involve the cerebral leptomeninges; (c) a pachymeningitis. In a case described by Fraenkel [7] there was a cervical osteomyelitis secondary to infection of a toe; the signs and symptoms of compression of the spinal cord developed; at necropsy the dura mater adjacent to the osteomyelitic focus was found to be thickened and infiltrated with round and plasma cells, among which there were many organisms resembling staphylococci; there was a definite compression of the spinal cord by the thickened dura; there was no epidural or subdural abscess.

Another complication is that of involvement of a major vascular trunk. In case 12, the purulent exudate, surrounding the right common iliac vein, produced a fatal thrombophlebitis. The inflammatory manifestations noted clinically in the right lower extremity were considered the result of retrograde phlebitis, although no substantiation by anatomic examination was undertaken at necropsy. There is a case described by Plenz [8] in which an intercostal vein, secondarily infected by pus from the dorsal vertebrae, was responsible for a bacteremia with metastatic abscesses and a fatal outcome. This thrombophlebitis had caused a swelling of the overlying soft tissues, which were red and tender. This, clinically, was thought to be due to the burrowing of pus from the diseased vertebrae. At operation no pus was found to explain the soft tissue swelling. The thrombophlebitis was neither suspected nor detected and yet was the most important inflammatory process present. A case of fatal erosion of an iliac artery has been reported.[9]

7. Fraenkel, E.: Ueber Spondylitis acuta infectiosa und Rückenmarkserkrankungen, Fortschr. a. d. Geb. d. Röntgenstrahlen 30:103 (Jan. 15) 1923.

8. Plenz, P. G.: Ueber Osteomyelitis acuta und subacuta der Wirbel, Deutsche med. Wchnschr. 47:416 (April 14) 1921.

9. Corret, P.; Michon, P., and Reny, F.: Abcès ostéomyélitique vertébral ayant ulcéré l'artère iliaque externe chez un ancien blessé de guerre, Rev. méd. de l'est 57:259 (May 1) 1929.

There are a number of complications recorded which depend on the location of the diseased vertebrae. In the cervical region the following may occur: (1) direct extension of the inflammatory process to the intracranial cavity, generally with fatal cerebral leptomeningitis [5]; (2) involvement of the roots of the phrenic nerve by the inflammatory granulation tissue or pus, with consequent paralysis of the diaphragm; (3) retropharyngeal abscess with respiratory obstruction, and (4) gravitation of the pus into the posterior mediastinum, with possible secondary perforation into a pleural or the pericardial cavity.

In the thoracic region there may occur: (1) perforation into the esophagus and (2) perforation into the mediastinum, with possible secondary perforation into a pleural or the pericardial cavity.

In the lumbar region the following may occur: (1) psoas abscess, the most common complication of lumbar osteomyelitis and already discussed, (2) perforation into the intestine, with consequent purulent diarrhea, and (3) perforation into the urinary tract, with sudden massive pyuria.

Although signs of peritoneal irritation are not infrequent, actual peritonitis is rare. It is most unusual for a psoas abscess to perforate into the peritoneal cavity.

RÔLE OF THE X-RAYS IN DIAGNOSIS

The x-rays were not of great service in demonstrating the presence of osteomyelitis. Only after bone destruction or new bone formation has occurred may one expect roentgenographic change. In eleven of the cases, roentgenograms were taken. In nine of these cases the examination was undertaken before operation or necropsy revealed the underlying pathologic process. In not a single one of these cases did the roentgenologist report evidence of acute osteomyelitis. The plates were either negative for bone disease or revealed nonspecific hypertrophic spondylitis. George and Leonard [10] also noted this tendency to rapid bone formation. The inflammatory processes in these cases varied in duration from at least a week to nine years. In three cases the roentgenograms were positive. In case 1, roentgenograms were taken one month after operation and showed evidence of osteomyelitis. In case 3, x-ray pictures were taken two days after operation and revealed crushing and fusion of three vertebral bodies, the underlying pathologic process being certainly more than two weeks old; the exact duration could not be ascertained. In case 5 roentgenograms were negative the day before operation, but were positive two and a half weeks after operation. Therefore, in a patient with vertebral

10. George, A. W., and Leonard, R. D.: The Vertebrae, Ann. Roentgenol. 8:70, 1929.

inflammatory disease the roentgenogram may be negative or reveal only evidence of hypertrophic spondylitis, despite the presence of an abscess in the bone, varying in estimated duration from ten days to four months. It is probable that many of the chronic cases (such as case 14 with gibbus formation) would show roentgen changes, but here the diagnosis is no longer in doubt. It may be that with more frequent roentgenographic examinations, the roentgenogram will prove to be of more value (see addendum).

PROGNOSIS

The prognosis is largely dependent on the following factors: A. The presence and nature of an existing complication. Involvement of the spinal cord offers the worst prognosis, and the formation of an abscess presenting in the back and resulting from a posterior perforation, the best prognosis.

B. The localization of the inflammation in the body or a process of a vertebra. In three of the cases presented, death was due indirectly to the local osteomyelitic focus alone, and in each instance the seat of the disease was in the body of the vertebra. In six cases there were concomitant abscesses in various viscera; in five of these cases, the body was the involved portion of the vertebra, while in the sixth the body of one and a process of another vertebra were involved. In three cases the processes were involved and in two others it is probable that the inflammatory process occurred in the processes. In four of these cases, uncomplicated by infection elsewhere, convalescence was uneventful. The fifth patient is in the hospital at present; his progress is satisfactory. In general, therefore, the involvement of the body carries with it a graver prognosis than does involvement of a process of a vertebra.

C. The promptness of the diagnosis and the adequacy of the surgical treatment.

D. The type of bacterium causing the infection. This does not play a considerable rôle; e. g., case 11, due to Streptococcus viridans, was fatal, while in case 10, due to a pneumococcus type I, and case 4, due to Staphylococcus aureus, the patients recovered.

E. The general resistance of the patient. Although it is undoubtedly a factor, it is difficult to evaluate.

TREATMENT

The treatment is surgical. Concerning it I wish to make only the following comment: A. The primary aim is to drain the suppurating area, especially in order to prevent complications due to perforation.

B. The focus in the bone itself must be drained; it is not sufficient to drain the complicating infection, e. g., an epidural abscess. Radical therapy may not be feasible when the patient is acutely ill, but it is nec-

essary for the accomplishment of a complete cure. Patton [11] described a case in point. In a case of thoracic osteomyelitis, there was removed only some necrotic bone, easily encountered, with the drainage of a small amount of pus. However, because of the progression of symptoms and the development of paraplegia, a second and more extensive operation was necessary after an interval of six weeks; on this occasion the diseased spinous processes and laminae and an exudate on the dura were removed, with the resultant disappearance of the paraplegia and a gradual complete cure.

C. The presence of metastatic foci does not contraindicate operation. The osteomyelitis may be the focus of the bacteremia. Cases of bacteremia with metastatic abscesses of the lung are not infrequent, in which, with the removal of the focus of the bacteremia, the abscesses in the lung heal spontaneously.

D. Recovery may occur after operation despite the presence of bacteria and a pleocytosis in the cerebrospinal fluid (case 6). Signs of compression of the spinal cord were present in this case and disappeared after the drainage of a collection of pus exterior to the vertebral column. Acute inflammatory compression of the spinal cord does not necessarily indicate the presence of more than edema of the epidural tissue and does not warrant a nihilistic attitude, even in the presence of evidence indicating an infected cerebrospinal fluid.

The mortality is still considerable. The following estimates are presented:

Makins and Abbott (Ann. Surg. **23**:510 [May] 1896)..71.4 per cent
Volkman (1914)....................................41.8 per cent
Borchers (1930)...56.3 per cent
Mount Sinai Hospital (1931).........................51 per cent
    (Case 5 excepted)

DIAGNOSIS

From what has been said, one can see how varied the clinical picture may be. The diagnosis must be entertained whenever any patient who has suffered from an infection presents signs and symptoms referable to a vertebral osteomyelitis. A patient who presents a history of a boil and in whom a sudden paraplegia develops must be investigated for epidural abscess. An apparently idiopathic abscess in the back must have its cause determined before meningitis occurs. One cannot dismiss the diagnosis because a bacterium not generally encountered in osteomyelitis has been obtained in culture. The acute nature (warmth, tenderness, redness, etc.) of the local inflammatory process should differentiate it from tuberculous spondylitis (Pott's disease). In the

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11. Patton, C. L.: *Acute Osteomyelitis of Spine*, Illinois M. J. **57**:268 (April) 1930.

literature, cases have been diagnosed as typhoid fever and cerebrospinal meningitis. In none of this series was this impression created. With the increase of bacteriologic knowledge, the presence of these diseases should be established rapidly. The most frequent diagnostic error has been the failure to consider the possibility of existence of vertebral osteomyelitis. A diagnosis of "toxic myelitis" should be made only after every effort has been made to rule out an epidural abscess.

SUMMARY

On the basis of sixteen cases, the subject of acute osteomyelitis of the vertebrae is presented with an analysis of the nature of the disease, its etiology, its pathogenesis, its clinical aspects, the value of roentgenograms in diagnosis, and some of the considerations underlying the prognosis and the therapeutic approach. The cases themselves are presented in detail as follows.

GROUP I. TYPE WITH ABSCESS FORMATION

CASE 1.—J. W., a man aged 31, was admitted to the hospital on May 6, 1925, with the history of a boil on the neck three weeks before admission, and pain over the left sacro-iliac region, first noticed two weeks before admission, spreading one week later to the left hip and thigh. Since the onset, the temperature had ranged between 100 and 103 F.; sweats had occurred every night, but there had been no chills.

Physical examination revealed tenderness and edema to the left of the lower lumbar vertebrae. Pain was spontaneous and increased on movement of the spine.

Course.—On May 10, there was a sense of deep fluctuation to the left of the fourth and fifth lumbar vertebrae. Aspiration yielded thick yellow pus. A diagnosis of osteomyelitis of the vertebrae was then made.

Operation.—On May 10, operation revealed an abscess cavity containing 4 drachms. (15.5 Gm.) of thick pus; in the floor of the cavity bare, rough bone was felt, which was interpreted as the left transverse process of the fifth lumbar vertebra. The cortex of this bone was removed.

Drainage was freed and convalescence uneventful.

Observations.—Bone removed at operation showed osteomyelitis.

Roentgen examination on June 9 showed rarefaction of the left upper articular process of the fifth lumbar vertebra, indicating a probable osteomyelitis.

CASE 2.—G. S., a 61 year old man, entered the hospital on Feb. 6, 1919, with a history of dull pain in the right thigh and lower part of the back for five weeks. Walking was difficult because of the pain.

Physical examination revealed a well nourished man, subacutely ill and supine, with the right hip flexed. Marked rigidity was present over the right half of the abdomen with an indefinite resistance in the right lower quadrant. On the right side of the lumbar spine were two masses, which were tender and fluctuant. The skin was reddened over them and there was marked edema of the entire lower part of the back. A Babinski sign was present on the right. The temperature was 102 F., the pulse rate 80 and the respiratory rate 20. The urine was normal.

Operation.—On February 8, an incision was made in the right costovertebral angle; several ounces of pus were obtained. The abscess cavity led down to roughened bone. On March 3, incision and drainage of the same abscess were again performed: rough bone was felt in the base of the abscess. A pocket of pus anterior to the spine was released and the wound curetted.

Course.—The temperature was normal thereafter and healing progressed uneventfully. The patient was readmitted on June 13. He was operated on twice on the second admission. On August 25, bare bone was felt with the curet. The patient was discharged on September 19, with the sinus healed. In 1921 there was a scant spontaneous discharge from the site of the scar, lasting one week; no operative indication was present.

Observations.—Urinalysis on Feb. 9, 1919, revealed no albumin or sugar; microscopic examination gave negative results.

Curettings removed at operation on March 19 showed chronic inflammatory tissue.

Roentgen examination showed: On Feb. 8, 1919, there was no evidence of a pathologic condition in the lumbar or the six lower dorsal vertebrae, except for a slight degree of spondylitis. On March 6, no evidence of pathologic condition in the lumbar vertebrae was noted. On April 2, the lumbar spine showed evidence of a slight spondylitis; however, a drainage tube present at the site of the right transverse process of the second lumbar vertebrae might have concealed a diseased area in the bone. On April 4, 1921, examination of the lumbar spine showed coalescence of the first and second lumbar vertebrae as seen in cases of old arthritis. On April 6, examination of the lumbar spine after the injection of bismuth showed the bismuth starting at the level of the fourth intervertebral space and reaching up as far as the transverse process of the second lumbar vertebra.

Case 3.—R. F., a boy aged 8 years, was admitted to the hospital on Aug. 18, 1925. He had had osteomyelitis of the right forearm and left femur four years before admission. Since then he had always been ailing. Two weeks before his admission, swelling and tenderness developed in the right lumbar region and he had an afternoon temperature of from 101 to 102 F.

Physical examination revealed, in addition to scars of previous operation on the right forearm and left thigh, a fluctuating, painful and tender mass, 2½ inches (6.3 cm.) in diameter, in the right lumbar region. The diagnosis was lumbar abscess secondary either to a renal abscess or to osteomyelitis of the spine.

Operation.—On August 19, incision and drainage of the abscess were performed. Bare bone was felt in the floor of the abscess cavity.

Course.—With adequate drainage, the wound did well and the patient was discharged on September 21, with only a slight discharge from the sinus tract. A follow-up note on Jan. 4, 1928, stated that the patient was well; no note was made concerning the lumbar region.

Laboratory Observations.—A blood count, on Aug. 19, 1925, showed white blood cells, 14,250; polymorphonuclears, 80 per cent.

A culture of pus from the abscess on August 19 revealed Staphylococcus aureus.

A roentgenogram on August 21 demonstrated evidences of a destructive process involving the bodies of the twelfth thoracic and first and second lumbar vertebrae, with crushing and fusion of these bodies.

Case 4.—I. S., a man aged 45, was admitted to the hospital on March 12, 1926, with the following history. Eighteen years before, he had had osteomyelitis of the right femur. Nine years later he was operated on, and a collection of pus was

found at the level of the first and second lumbar vertebrae behind the psoas muscle. No culture of this pus was taken. For three weeks prior to admission he had been suffering from pain in the back, progressive in nature and accompanied occasionally by fever.

Physical examination revealed evidences of mitral stenosis and insufficiency, probably rheumatic, and swelling, tenderness and spasm of the muscles to the left of the scar of the previous operation in the lumbar region. The temperature was 106 F. The diagnosis was exacerbation of an old osteomyelitis with spontaneous perforation along the scar of the previous operation.

Operation.—On March 15, an incision was made over the swollen area and pus obtained. In the base of the cavity pus was seen oozing from the bone. The necrotic bone was chipped away and the cavity drained.

Course.—The wound did well, and with a minimal discharge still present, the patient was discharged to the care of his private physician.

Laboratory Observations.—Culture of pus revealed Staphylococcus aureus.

The necrotic bone removed at operation was reported as showing evidences of acute osteomyelitis.

On March 13, 1926, roentgen examination of the lumbodorsal spine showed only evidences of hypertrophic spondylitis. In the anteroposterior position the fourth lumbar vertebra did not appear to be normal. However, in the lateral position, nothing was seen to support this view.

CASE 5.—L. G., a 51 year old man, was admitted to the hospital on Feb. 11, 1932. For seven months prior to admission he had had a discharging right otitis media. Four months prior to admission, the right preauricular region of the face was swollen for two weeks. Shortly after this the patient began to suffer from pain in the left flank and left costovertebral angle. There was fever with chilly sensations for eleven weeks prior to admission. A blood culture at another hospital three months before had revealed the pneumococcus type III.

Physical examination revealed a chronically ill looking man who could not move about because of pain in the lumbar region of the back. Both ear-drums were intact. A few shotty lymph nodes were palpable in the right anterior cervical region. The right costovertebral angle was tender, bulging and fluctuant. The left costovertebral angle was full and tender. There was shock tenderness over the lumbar spine. The diagnosis of osteomyelitis of the lumbar vertebrae was made.

Operation.—On February 13, the right and left lumbar spaces were incised. On the right side an abscess cavity containing 8 ounces (226 Gm.) of pus and a sequestrum of the right transverse process of an upper lumbar vertebra were found. On the left side an abscess cavity was encountered at the bottom of which a denuded transverse process of an upper lumbar vertebra was found. There was a communication between the abscesses across the anterior aspect of the spine.

Course.—The patient is still in the hospital with the operative wounds draining. His condition is satisfactory. Exploration of the right transverse sinus on March 13 showed complete obliteration of the sinus owing to a healed thrombophlebitis.

Observations.—A blood count on Feb. 12, 1932, showed: hemoglobin, 47 per cent; red blood cells, 2,890,000; white blood cells, 21,000; polymorphonuclears, 76 per cent.

Urinalysis showed: specific gravity, 1.012, acid, a few single white blood cells and no albumin.

A blood culture on Febrary 12, was sterile. A smear of pus obtained at operation, on February 13, showed gram-positive cocci; no tubercle bacilli were seen.

A culture yielded the pneumococcus type III. A culture of the urine on February 13 showed the pneumococcus type III and Staphylococcus albus.

Roentgen examinations were as follows: On February 12, examination of the spine showed no evidence of osteomyelitis. There was moderate hypertrophic spondylitis of the lower dorsal and lumbar bodies. On March 2, reexamination of the lumbosacral spine showed almost complete disappearance of the right transverse process of the second lumbar vertebra, and an exaggeration of the spondylitis, involving the second and third vertebrae. There was marked clouding of the entire right mastoid process.

Comment.—This is considered to be a case of otogenic sepsis, due to the pneumococcus type III, consequent on a latent spontaneously healing thrombophlebitis of the right transverse sinus, with metastatic infection of the lumbar vertebrae.

CASE 6.—R. V., an infant 2 months of age, was admitted to the hospital on Sept. 10, 1923, with the history of a bluish swelling on the back of the neck, present at birth; this became hard and two weeks later discharged pus, which continued to drain up to the time of admission. For six days before admission, fever had been noticed. For five days the infant had not been able to move her left arm.

Physical examination revealed a reddened area of induration on the posterior aspect of the neck. The infant could not move either arm. The upper extremities showed flaccid hypotonia with anesthesia. The right lower extremity was spastic. Aspiration of the swelling yielded a few drops of pus.

Operation.—On September 12, operation revealed a large collection of pus under tension, deep to the erector spini muscles; in the base of the abscess rough bone was exposed, which was thought to be the left transverse process of the fifth or sixth cervical vertebra.

Course.—The wound healed satisfactorily, the motor and sensory disturbances cleared up and the patient was discharged. Convalescence was uneventful except for a period of aggravation of the symptoms of infection with transient bacteremia about September 22.

Laboratory Observations.—A blood count on Sept. 11, 1923, showed: white blood cells, 40,200; polymorphonuclears, 54 per cent.

A blood culture on September 14 was sterile. On September 22, a culture revealed 200 colonies of Staphylococcus aureus per cubic centimeter.

Cultures of the cerebrospinal fluid showed: on September 12, 24 cells and sterile fluid; on September 22, Staphylococcus albus and Streptococcus anhemolyticus; on September 23, 2 cells; on September 28, sterile fluid; on September 29, sterile fluid.

A smear of the pus from the abscess of neck removed at operation on Sept. 12, 1923, was negative; a culture was sterile.

Comment.—The nature of the swelling present on the back of the neck was not definitely ascertainable. There was no evidence to indicate that a meningocele existed. The primary condition was probably a hematoma, possibly resulting from birth trauma, which became secondarily infected.

CASE 7.—R. A., a woman aged 58, was admitted to the hospital on Dec. 12, 1927, with the history of a sudden onset of pain in the right knee radiating up to

the groin, three months before admission. This persisted, was constant and lancinating and was aggravated by motion and damp weather. At the same time, the patient noted a swelling in the right groin, which was very tender and increased in size. The temperature varied from 100 to 104 F. throughout the three months. There was a loss of 30 pounds (13.6 Kg.), in three months. Roentgenograms of the spine taken outside the hospital were said to have been negative. (There was a vague history of osteomyelitis of the right twelfth rib twenty years before.)

Physical examination revealed a cachectic woman with swollen, tender right inguinal lymph nodes; the abdomen relaxed; there was no tenderness and no masses were palpable. The right knee was flexed and there was pain on extension referred to the groin. There was a small well healed scar over the right twelfth rib. The diagnosis made was that of hidden malignant neoplasm with metastases to the right groin.

Course.—On December 17, spasm of the right psoas muscle was noted, so that abscess of that muscle was suspected. The temperature rose; the patient did poorly and died on December 20.

Laboratory Observations.—A blood count showed: white blood cells 8,300; polymorphonuclears, 80 per cent.

The urine contained no albumin, sugar, casts or red or white blood cells.

A roentgenogram of the spine, taken on Dec. 19, 1927, was reported as showing a marked degree of hypertrophic spondylitis between the bodies of the twelfth dorsal, first lumbar and transverse processes of the second, third and fourth lumbar vertebrae on the left side. The left twelfth rib was markedly thickened and irregular, with areas of possible destruction. The eleventh rib also showed similar changes. The appearance of the bones suggested an inflammatory rather than a malignant process.

Autopsy.—Postmortem examination revealed a large retroperitoneal abscess along the course of the right psoas muscle containing 1 liter of greenish pus, compressing and destroying the psoas muscle. The posterior wall of the abscess was formed by dense scar tissue extending upward to the eleventh rib. The bodies of the third and fourth lumbar vertebrae were found to be eroded. The body of the third lumbar vertebra contained a rather old abscess lined by a membrane of granulation tissue near the posterior surface. There were several small abscesses in the fourth lumbar vertebra.

Pus from the psoas abscess contained hemolytic streptococci and B. pyocyaneus on culture; smear showed only gram-positive cocci in chains.

Comment.—This, then, was a case of purulent osteomyelitis of the lumbar vertebrae with the formation of a tremendous retroperitoneal abscess. The primary focus may have been an osteomyelitis of the twelfth rib on the right side, twenty years before. However, the existence of this lesion was not definitely remembered. At autopsy the ribs were not examined.

CASE 8.—L. A., a woman aged 44, was admitted to the hospital on Nov. 21, 1928. She had a history of diabetes for ten years. Two years prior to admission, she suffered from a carbuncle of the neck subsequent to which there was a series of abscesses in the right foot and leg, left leg, right clavicular region and left thigh. She entered because of pain in the right hip, knee and leg, with anorexia and vomiting for three weeks.

Physical examination revealed an undernourished, undersized woman with tenderness over the right costovertebral angle and over the spinous process of the twelfth thoracic and first and second lumbar vertebrae. The diagnoses made were abscess of the right psoas muscle and osteomyelitis of the left tibia with subperiosteal abscess.

Operation.—Five ounces (141 Gm.) of pus was evacuated from the abscess of the right psoas muscle; bare bone was not felt. Incision and drainage of the subperiosteal abscess of the left leg were also performed.

Course.—Both wounds discharged large amounts of thick pus. Postoperatively, the patient did poorly. The diabetes was not controlled well, and at one time the patient sank into stupor with ketosis, from which she was resuscitated. On Jan. 27, 1929, pain over the lower cervical spine was noticed. There was edema of the face and hands. A week later the patient began to complain of pain in the neck. There was swelling with some induration over the lower cervical region with a sense of deep fluctuation. There was marked local tenderness with pain on motion. On January 16, incision and drainage of a posterior cervical abscess, apparently extending to the spinous process of the seventh cervical vertebra, were performed. The patient did poorly and died on February 6.

Laboratory Observations.—A culture of pus from the abscess of the psoas muscle on Nov. 27, 1928, revealed Staphylococcus albus. A culture of pus from the subperiosteal abscess of the left leg on November 27 revealed Staphylococcus albus. A culture of pus from the cervical abscess on Jan. 27, 1929 revealed Staphylococcus aureus.

A roentgenogram taken on Nov. 24, 1928, showed bony abscesses in the left tibia. On Jan. 14, 1929, a roentgenogram of the cervical spine showed no abnormality in the bones, although there was an absence of the normal cervical lordosis. Whether this was due to the posture of the patient or to an inflammatory process could not be stated.

Autopsy.—Postmortem examination revealed an abscess cavity, 1 cm. in diameter, in the right transverse process of the third lumbar vertebra. From this region pus extended beneath the muscles along the inner surface of the ilium. It was this area behind the psoas muscle which had been drained by the operation. There was also osteomyelitis of the fifth cervical vertebra and of the left tibia. In addition, there were multiple metastatic abscesses of the right kidney, heart and lungs, with pyopneumothorax.

Comment.—This case was that of a patient with long-standing diabetes on whom a carbuncle developed, with resultant bacteremia and metastatic abscesses situated in the viscera and bones.

CASE 9.—D. R., a woman aged 59, was admitted to the hospital on Oct. 7, 1928, with a history of infection of the respiratory tract four weeks before admission, lasting ten days, ending by crisis and diagnosed by her physician as "pneumonia." Three weeks before admission she began to experience a dull ache in the right buttock, accompanied by tenderness on pressure, local heat and swelling. These symptoms progressed in severity up to the time of admission.

Physical examination revealed a circumscribed swelling of the right buttock with questionable fluctuation. No redness over the swelling and no glycosuria were observed. A diagnosis of abscess of the buttock was made.

An operation was performed on October 7. A large abscess cavity containing thick, greenish pus was found extending mesially to the periosteum over the sacrum, which was apparently intact.

Course.—The abscess was draining satisfactorily and the patient was doing well when, on October 24, she had a chill lasting twenty minutes and later complained of abdominal pain and tenderness. The same day, tenderness and distention became marked, and signs of fluid in the abdomen were present. Abdominal puncture was performed and pus obtained. The patient died the next day, October 25.

Laboratory Observations.—A blood count on October 24 showed: white blood cells, 13,600; polymorphonuclears, 83 per cent.

The urine was normal.

A smear of fluid obtained by abdominal puncture showed gram-positive diplococci surrounded by capsules. In a culture of abdominal pus (obtained on October 24) the pneumococcus type IV was grown.

Autopsy.—Postmortem examination revealed small necrotic abscesses in the bony substance of the third and fourth lumbar vertebrae. These communicated by a fistulous tract with the incision in the right buttock. There were also fresh adhesions over the right lower lobe of the lung. There was a generalized purulent peritonitis, consequent on perforation of a secondarily infected echinococcus cyst of the liver. A culture of pus from the vertebral abscess revealed the pneumococcus type IV.

Comment.—This is a case of respiratory infection, probably pneumonia of the right lower lobe (fresh adhesions were found there post mortem), with bacteremia, metastatic infection of the third and fourth lumbar vertebrae and a preexisting echinococcus cyst of the liver. The latter ruptured and produced a fatal peritonitis. Of interest are the following considerations:

1. The condition presented itself as an abscess of the right buttock. The etiology, namely, osteomyelitis of the vertebrae, was not established at operation nor was it suspected clinically.

2. No mention was made of tenderness over the spine in the physical examination.

Case 10.—I. F., a youth, aged 19, was admitted to the hospital on March 11, 1928, with a history of severe pain in the right ear a month before admission. The day after the onset of the pain, myringotomy was performed and a thin purulent discharge escaped from the middle ear. The patient was doing well until three days before admission, when the discharge ceased. Two days later he again had severe pain in the right ear with a thick discharge, thicker and more profuse than previously. One week before admission he had had a chill lasting five minutes.

Physical examination revealed an acutely ill young man, with a temperature of 103.4 F., a thick, purulent discharge from the right middle ear, sagging of the canal wall and impairment of hearing. The diagnosis of acute mastoiditis was made.

Operation.—The patient was operated on on March 11. The mastoid process contained a few scattered small abscesses with little breaking down of the bone.

Course.—On March 12, there was a chill. The patient complained of headache and a bilateral Kernig sign was present. On March 13, the patient began to complain of pain in the right upper quadrant of the abdomen. This was considered pleuritic. On March 16, a pleural friction rub was heard over the right side of the chest anteriorly with diminished breath sounds. Thereafter dulness developed over

the right side of the chest posteriorly. On March 30 an abscess in the right buttock, which had gradually been forming, was incised and drained. On April 19, there was tenderness of the spinous processes of the seventh and eighth dorsal vertebrae. On April 10, pus was aspirated from the right side of the chest posteriorly.

Operation.—On April 10, thoracotomy was performed with resection of the seventh and eighth ribs on the right side. A well encapsulated cavity was found the lateral wall of which was interpreted as the external surface of the parietal mediastinal pleura. The mesal limit was the under surface of the ribs noted, and the anterolateral aspects of the bodies of the seventh and eighth dorsal vertebrae were laid bare. There was a recess leading to the body of the seventh vertebra, but at that point bare bone could not be felt. In contrast to the other, this vertebral body was tender to pressure. The abscess cavity was drained, and the patient recovered completely after an uneventful convalescence.

Laboratory Observations.—On March 11, 1928, pus from the middle ear yielded the pneumococcus type I on culture. A blood culture on March 12 revealed the same organism. Three subsequent blood cultures were sterile. A culture of pus from the abscess in the buttock on March 30 was reported as showing gram-positive diplococci overgrown by Staphylococcus albus. Pus from the mediastinal abscess on April 10 revealed the pneumococcus type I.

On March 19, a roentgenogram of the chest showed a shadow extending anteriorly from the mediastinum, considered to be a partial consolidation of the mesial half of the right lung. On April 3, a roentgenogram of the chest showed this shadow to be more extensive, denser and more sharply demarcated.

Comment.—This is interpreted as a case of acute mastoiditis with transient bacteremia after mastoidectomy, consequent metastatic abscess of the seventh thoracic vertebra, perforation and a resultant mediastinal abscess.

GROUP II. TYPE WITH SYMPTOMS OF DISEASE OF THE NERVOUS SYSTEM

CASE 11.—A. D., a woman, aged 47, had a cholecystectomy performed in October, 1926. At that time the operating surgeon reported the presence of only a single large gallstone. The patient was well until March, 1927, when she began to suffer from severe pain in the right upper quadrant of the abdomen, chills, fever and jaundice. In May, she was operated on at another hospital for the relief of these symptoms. However, a few weeks before her admission on Feb. 29, 1928. she began to suffer from abdominal pain, chills and fever.

Physical examination revealed an acutely and chronically ill woman, with jaundice, a temperature of 103.8 F., two operative scars in the right upper quadrant of the abdomen and some tenderness in the epigastrium. The diagnosis was obstruction of the common bile duct with cholangeitis.

Operation.—On March 3, the patient was operated on; a large mass of exudate was found around the common duct and porta hepatis. The common duct was dissected free and a tube placed in it, resulting in the immediate escape of bile.

Course.—Postoperatively, although there was adequate drainage of bile, the patient continued to have a high septic temperature, fluctuating between 99 and 105 F. On March 22 she began to complain of pains and paresthesias in both legs.

Knee jerks and ankle jerks were absent. There were tenderness of muscles and along the nerve trunks and impaired sensory perception, involving chiefly pain, temperature and deep muscle sensibility in both lower extremities. The diagnosis was toxic neuritis due to the long-standing infection. On March 24, the patient began to suffer from inability to void properly. On March 28, it was noted that she had a subfebrile temperature with occasional attacks of high fever. There was marked paresis of both lower extremities with beginning foot-drop, loss of both knee jerks and ankle jerks, loss of all forms of sensation in the left leg from the midcalf down and in the right leg from the knee down, and tenderness over the second and third sacral vertebrae. On March 31, the diagnosis made was epidural abscess with secondary involvement of the spinal cord at the level of the tenth dorsal vertebra. On April 1, the temperature began to mount again, the patient complained of headache, there was some rigidity of the neck and the general condition was poorer. The Queckenstedt test was performed, with the needle in the third lumbar interspace. The impression was that no block existed. Cerebrospinal fluid removed showed evidence of meningitis, but there were no clinical indications of cerebral infection. A Queckenstedt test performed on April 3 indicated the probable presence of spinal cord block. On April 4, the mentality was still clear. The next day the patient became irrational, irresponsive and later stuporous; the pulse became rapid and feeble, and death occurred on April 5.

Laboratory Observations.—A blood count on March 12, 1928, showed: white blood cells, 5,000; polymorphonuclears, 48 per cent.

Urinalysis on March 1 revealed bile, urobilin, albumin and white blood cells.

On March 1 a blood culture showed Streptococcus viridans; on March 5, no growth, on March 12, Streptococcus viridans.

On April 1, the cerebrospinal fluid was turbid and contained 10,000 cells per cubic centimeter, with 98 per cent polymorphonuclear leukocytes. Only gram-positive cocci were seen on smear. These failed to grow in cultures.

Autopsy.—Postmortem examination revealed a purulent cholangeitis with multiple abscesses of the liver, one of which had invaded the main right hepatic vein, causing thrombophlebitis at that point. One centimeter from the porta hepatis there was complete stricture of the common bile duct. There were widespread metastatic abscesses in the viscera. The third lumbar vertebra was the seat of a wedge-shaped area of necrosis communicating with the epidural space. There was an epidural abscess extending from the third lumbar to the ninth thoracic vertebra. The body of the second lumbar vertebra presented several softened areas in the bone communicating with the spinal canal by means of a perforation through which a probe could be passed. Exposure of the spinal canal, in so far as it was possible, revealed the presence of a subdural abscess extending from the cauda equina to the highest point of the incision permitted (the limit was not stated; it was probably up to the midthoracic vertebrae). There was also a purulent leptomeningitis. A smear of the pus from the vertebrae revealed gram-negative bacilli (probably a postmortem invader). Cultures were not taken.

Comment.—This case was one of stricture of the common bile duct with resultant cholangeitis and cholangeitic abscesses of the liver, thrombophlebitis of the hepatic vein with resultant bacteremia and multiple metastatic abscesses. Some of these had occurred in the bodies of the second and third lumbar vertebrae, whence there occurred perforation into the epidural, then into the subdural and finally into the

spinal subarachnoid space, causing fatal leptomeningitis. This case was diagnosed in vivo. Of interest are the following considerations:

1. Clinically, tenderness had been elicited over the spinous processes of the second and third sacral vertebrae; however, at postmortem examination the osteomyelitic foci were found to be in the second and third lumbar vertebrae.

2. The first indication of the presence of vertebral disease was that of pressure on the nerve roots.

3. Although examination of the brain was not permitted at necropsy, undoubtedly a cerebral leptomeningitis must have been present. The spread of the infection from the spinal to the cerebral leptomeninges could be followed by parallel changes in the clinical condition of the patient, i. e., at first only signs of spinal cord disease and later the headache, irrationality, and stupor of cerebral disease.

CASE 12.—I. G., a 43 year old man, with a known history of diabetes for six months, entered the hospital because of pyuria, frequency and dysuria, beginning two months before admission. Later there developed urinary retention and dribbling. For two weeks there were numbness and weakness of both lower extremities, progressive up to the time of admission. Eight days before admission a bedsore developed over the sacrum.

Physical examination revealed a weakened, chronically ill looking middle-aged man. There was a large decubitus ulcer over the sacrum and buttocks. Below the level of the seventh dorsal vertebrae there was a loss of all sensation, muscular power and deep reflexes. The patient was considered to be suffering from a transverse myelitis, toxic in nature, due to cystitis.

Course.—The patient did poorly, and died the day after admission.

Laboratory Observations.—The urine contained a large amount of pus.

Autopsy.—There was a purulent cystitis with a prostatic abscess. In addition, there was an epidural abscess extending from the ninth dorsal to the sixth cervical vertebrae with extension into the right thoracic cavity and consequent fibrino-purulent pleurisy. In the muscle there was a walnut-sized abscess just opposite the intervertebral foramen between the spinous and right transverse processes of the ninth dorsal vertebra which had perforated into the epidural space. No evidence of osteomyelitis was found.

Comment.—This is interpreted as a case of purulent prostatitis with a metastatic abscess, situated in the muscle immediately opposite an intervertebral foramen, which perforated into the epidural space. Of interest are the following considerations:

1. The complication, epidural abscess, may so dominate the clinical picture that the primary etiologic condition may be clinically silent. On examination of the patient, it may be impossible to differentiate a case such as this one from one of epidural abscess secondary to osteomyelitis of the vertebra.

2. Osteomyelitis of the vertebra is not the only cause of epidural abscess.

GROUP III. TYPE WITH PAIN IN THE BACK AND FEVER

CASE 13.—C. G., a woman, aged 56, was admitted to the hospital on Sept. 11, 1930, with a history of an infection of a finger of her left hand four months before. This was followed by swelling, tenderness and redness of the entire left arm, chills, a temperature up to 106 F. and general weakness. The diagnosis was erysipelas. The fever subsided after ten days, and there followed slight desquamation of the skin of the arm. For two weeks thereafter the patient was weak. Two weeks later (three months before admission), she began to have a sharp hammering pain beginning in the sacral region, extending to both hips and thighs, occurring daily, worse at night, aggravated by motion and baking, and relieved only by drugs taken on the day before admission. Eight days before admission she was seized with a severe paroxysm of pain in the neck necessitating her going to bed. That night there was delirium. Thereafter there were a high temperature, ranging from 101 to 105 F., profuse sweats and loss of appetite. The day before admission the patient began to suffer from dyspnea and cough, with only slight expectoration.

Physical examination revealed an acutely ill woman, aged 56, who breathed rapidly, with a slight expiratory grunt, coughed occasionally, without the production of sputum, and had flushed cheeks. The temperature was 102 F., the pulse rate 110 and the respiratory rate 26. There was some dulness, with numerous coarse clicking râles over the base of the right lung where the breath sounds were somewhat diminished. There were no signs of fluid or tenderness of the ribs. There was tenderness in the right costovertebral angle. There was some tenderness on percussion over the lumbosacral and sacro-iliac articulations. The diagnosis made was that of bronchopneumonia of the right lower lobe and chronic sacro-iliac arthritis.

Course.—The clinical signs over the right lower lobe persisted unchanged. Because of tenderness over the right costovertebral angle, the diagnosis of metastatic abscess of the right kidney was temporarily entertained. About a week after admission, the patient began to have tenderness in the region of the liver. It was thought that she might have osteomyelitis of the rib and, therefore, two aspirations were made (September 18) at the level of the right fourth rib without encountering pus. A day later the patient began to complain of pain in the legs. There was cutaneous hyperalgesia present but no definite evidence of a spinal cord lesion. There was no appreciable tenderness over any portion of the vertebral column. There was a persistent plateau temperature, averaging about 104 F. On September 19, a diffuse, tender, erythematous pitting induration was seen on the posterior aspect of the right leg. This process spread progressively up to the thigh. On September 20, the patient had a slight chill, which was the first observed since admission. On September 21, exploratory aspiration of the right groin was performed; there was no pus, but some oily droplets were obtained. The patient became jaundiced, sank into stupor and died on September 22.

Laboratory Observations.—A blood count on September 11 showed: white blood cells, 18,700; polymorphonuclear leukocytes, 84 per cent.

Urinalyses on September 11 to 20 showed albumin, one plus, and a few single and very few clumped white blood cells.

Cultures of the urine on September 11, 17 and 20 yielded B. coli. A blood culture on September 11 was sterile; on September 16 a culture yielded 33 colonies of Streptococcus hemolyticus per cubic centimeter; on September 21, 225 colonies of Streptococcus hemolyticus per cubic centimeter.

On September 12, a roentgenogram of the chest showed thickening of the pleura over the right lower lobe with possible calcification. On September 16, a roent-

genogram of the abdomen, taken because of the postulated diagnosis of right peri-
nephritic abscess, revealed only dilated bowel containing much gas.

Autopsy.—Postmortem examination revealed a suppurative spondylitis and peri-
spondylitis involving the bodies of the fifth lumbar and first sacral vertebrae, with
softening and purulent destruction of the intervening intervertebral disk. This
process had spread anteriorly, causing a suppurative inflammation of prevertebral
fatty tissue with suppurative thrombophlebitis of the right common iliac and
external iliac veins.

Comment.—This is interpreted as a case of osteomyelitis of the
vertebrae consequent on a bacteremia, probably present at the time of
the infection of the left arm four months before admission. The sup-
purating focus perforated anteriorly and produced a purulent thrombo-
phlebitis of the right common iliac vein with consequent overwhelming
bacteremia and a fatal outcome. In the light of the postmortem knowl-
edge, the process in the right calf, noted clinically, was considered to be
due to retrograde phlebitis of the veins of the right lower extremity,
although this was not definitely determined at necropsy. Of interest
are the following considerations:

1. Although there was some tenderness over the sacrum and the
sacro-iliac joints on admission, this did not increase and was not more
marked than that elicited over the rest of the spine.

2. A flat x-ray plate of the abdomen was taken on September 16,
because one of the diagnoses under consideration was a right peri-
nephritic abscess. While it is true that this roentgenogram was not
taken for the specific purpose of detecting the presence of osteomyelitis
in the lumbosacral spine, nevertheless, at the time the roentgenogram
was taken, the patient undoubtedly had had the inflammatory process
in the vertebrae for about four months; yet on retrospect considera-
tion of the x-ray plate, no evidence of disease in the fifth lumbar or
first sacral vertebra (no lateral view) could be seen.

3. There was no clinical index of local inflammatory disease except
the complaint of pain.

GROUP IV. TYPE WITH WIDESPREAD SUPPURATION

Case 14.—D. A., a man, aged 60, was admitted on Oct. 5, 1926, with a history
of severe pain in the left side of the abdomen and back, chills, fever and profuse
sweats for three days.

Physical examination revealed a well developed man of 60, not looking espe-
cially ill; the tongue was coated and the pharynx reddish and dry; dulness and
numerous moist râles were noted at the base of the right lung posteriorly and an
inconstant sense of resistance in the right upper quadrant of the abdomen; the liver
could be percussed three fingerbreadths below the right costal margin. The tempera-
ture was 98.2 F., the pulse rate 78 and the respiratory rate 20. The blood pressure
was 122 systolic and 80 diastolic. The diagnosis of resolving bronchopneumonia at
the base of the right lung was made.

Course.—On October 6 the patient had a chill with a rise in temperature to 104 F. Tenderness and spasticity over the right side of the abdomen and the right lumbar region were noted. A catheterized specimen of urine contained pus and a faint trace of bile. The diagnosis of right pyonephrosis was made. On October 8, a chill occurred. On October 9, cystoscopy with ureteral catheterization showed numerous white blood cells coming from both kidneys, with a few clumps of white blood cells from the right side. On October 11, herpes labialis appeared; a note was made of thick tenacious sputum. On October 13 and 20, a chill occurred. On October 21, the suspicion of a right subphrenic abscess was entertained; the right half of the diaphragm moved less than the left. The liver and subphrenic space were aspirated; no pus was encountered. On November 1, the patient had a severe shaking chill. He complained of pain in the right upper quadrant. The only physical finding elicited in the abdomen was voluntary spasm. Later that day, tenderness and a mass in the right upper quadrant developed, the conjunctivae became icteric and the liver was tender to percussion. A hepatic abscess was suspected. Bile was found in the urine the next day. On November 12 there was no disturbance in motion of the right side of the diaphragm and no tenderness over the liver on jarring. On November 20 the patient complained of pain in the lower part of the back. On November 28 he had severe pain in, and marked tenderness over, the sacrum. A low grade fever persisted. There was a varying leukocytosis.

The patient was discharged at his own request on December 2. He was readmitted on Jan. 26, 1927. He was emaciated and moribund, and kyphosis had developed over the lower part of the spine since his discharge. In the interim he had been fairly well, and had spent most of the time in bed; the only complaint was pain in the back on rising. On the day of admission, he had two severe chills, followed by profuse sweats. The temperature was 104 F., the respiratory rate 30 and the pulse rate not obtainable. The patient did poorly and died a few hours after admission.

Laboratory Observations.—Blood counts showed: on October 6, 1926, white blood cells, 41,800, and polymorphonuclears, 92 per cent; on October 7, white blood cells, 24,400, and polymorphonuclears, 94 per cent; on October 16, white blood cells 10,400, and polymorphonuclears, 76 per cent; on November 11, white blood cells, 29,000, and polymorphonuclears, 88 per cent; on November 29, white blood cells, 20,000, and polymorphonuclears, 86 per cent.

On Oct. 7, 1926, a culture of the blood yielded the Friedländer bacillus, 300 colonies per cubic centimeter in twelve hours. On the patient's readmission on Jan. 26, 1927, a culture showed: 145 colonies of the bacillus per cubic centimeter in twelve hours. On Oct. 8, 1926, a culture of the sputum yielded the Friedländer bacillus. In cultures of the urine on October 12 to 20 the Friedländer bacillus was found three times. The Wassermann reaction of the blood was negative.

From Oct. 6, 1926, to the time of the patient's discharge urinalysis repeatedly showed many white blood cells, often clumped. The reaction to the albumin test was always one plus. On November 2, bile and urobilin were present; on November 3, bile.

On Oct. 6, 1926, a roentgenogram of the chest showed deficient aeration of the base of the right lung perhaps due to a recent pneumonia. The right side of the diaphragm was slightly elevated. On October 12, the lungs showed no abnormality; the right side of the diaphragm was somewhat elevated, but not sufficiently to warrant the diagnosis of a subphrenic abscess. On November 13, the dorsolumbar spine showed a marked degree of hypertrophic spondylitis. On November 20, a roentgenogram of the chest revealed few small infiltrations of a resolving pneumonia at the base of the right lung.

Autopsy.—Postmortem examination revealed an emaciated man with a kyphosis in the region of the first lumbar vertebrae. The lungs were normal except for fibrous pleural adhesions. In the abdomen, between the hepatic flexure of the colon, liver, gallbladder and first portion of the duodenum, there was a loculated abscess containing thick green pus. In the papilla of Vater was a facetted pigment stone, 15 mm. in diameter; the common duct was not inflamed, but was greatly dilated (30 mm. wide when open) and filled with greenish-yellow pus. A few other stones were found in the bile passages. The neck of the gallbladder opened directly into an abscess in the right lobe of the liver adjacent to it, the size of a large apple. This contained greenish pus, and its wall consisted of a shaggy necrotic membrane. Parts of the necrotic walls of the gallbladder were still attached to portions of the wall of the abscess. A direct extension of the hepatic duct entered the abscess cavity. One of the smaller branches of the left division of the portal vein lying in the abscess area had become invaded and contained a purulent thrombus, which extended a considerable distance proximal and distal to its seat of primary involvement by retrograde thrombosis, but the main stem of the portal vein was free.

The kidneys were macroscopically normal; microscopically they showed cloudy swelling, infiltration of the stroma with lymphocyte and leukocyte cells and the formation of many small abscesses.

The prevertebral tissue in the region of the lumbar spine was thickened and suppurated. The first lumbar vertebra was in part destroyed, including the inter-vertebral disk between the first and second lumbar vertebrae.

A culture of pus from the hepatic abscess and first lumbar vertebra showed Friedländer's bacillus (Bacterium mucosum-capsulatum) in all cultures. Smears showed pus and gram-negative bacilli.

Comment.—In this case one cannot be certain whether the suppurative cholangeitis, due to Bact. mucosum-capsulatum, was primary or whether there first occurred a pneumonia caused by that organism, with bacteremia and metastatic infection of the biliary passages, obstructed by calculi in the common bile duct. The abscess of the liver was probably secondary to cholangeitis. Although no gross thrombophlebitis of the hepatic vein radicles was demonstrated, the hepatic abscess was probably the cause of the bacteremia leading to the renal and vertebral abscesses. However, all the pathologic processes found at necropsy may have been due to a bacteremia at the onset of the disease with a pneumonia due to Bact. mucosum-capsulatum. Of interest are the following considerations:

1. The unusual occurrence of a case of osteomyelitis due to Bact. mucosum-capsulatum (Friedländer's bacillus).

2. The acute development of a gibbus due to suppurative non-tuberculous spondylitis.

CASE 15.—J. R., a man, aged 30, was admitted to the hospital on Oct. 13, 1930, with the history that ten days before admission a boil developed on the back of the neck, which he squeezed during the subsequent two or three days. This was followed by complete healing of the abscess a few days later. Four days before admission, a mild pain developed in the interscapular region which rapidly became worse. On motion, the patient had sharp pain locally, with radiation down the left

side. On the next day he began to feel feverish. One day later, two days before admission, he had a shaking chill lasting an hour, which was repeated the night before admission. For the three days prior to admission, he had marked anorexia, general malaise, headache, profuse sweating and constipation.

Physical examination revealed an acutely ill man complaining of pain in the midthoracic spine. There was the scar of a well healed abscess on the back of the neck. Flexion of the neck was limited by pain in the midthoracic region, presumably due to spasm of the muscles. There was a short systolic murmur at the apex. No diastolic murmurs were heard. There was some fulness of the prostate with questionable tenderness. There was exquisite tenderness over the *spinous* process of the fifth thoracic vertebra with some tenderness over the spinous processes of the fourth and sixth thoracic vertebrae. To the right of the fourth thoracic vertebra there was some slight tenderness and fulness of the soft tissue. There was bilateral costovertebral tenderness. The diagnosis was Staphylococcus aureus sepsis with metastasis to the spine (fifth thoracic vertebra).

Course.—On October 14 a Kernig sign developed on the left, the knee jerks were depressed and the upper abdominal reflexes were diminished. Abdominal reflexes were not elicited on October 15. At this time, a prominence of the soft tissue was seen to the left of the spine at the level of the fourth and fifth thoracic vertebrae, construed as indicating deep suppuration.

Operation.—The patient was operated on on the night of October 15. There was no free pus found to correspond to the swelling of the soft tissue. The laminae of the fourth, fifth and seventh thoracic vertebrae were removed; the fifth thoracic seemed definitely sclerosed. An extensive epidural abscess was encountered and drained.

Course.—The patient did not do well, and died on October 19, three days postoperatively.

Laboratory Observations.—A blood count on October 13 showed: white blood cells, 18,000; polymorphonuclears, 78 per cent.

On October 14 the urine showed albumin, one plus, but was otherwise normal.

Cultures of the blood showed: on October 13, 7 colonies of Staphylococcus aureus per cubic centimeter; on October 17, Staphylococcus aureus colonies too numerous to count.

On October 14, a roentgenogram of the spine showed evidences of an old lesion at the level of the fourth and fifth thoracic vertebrae with resultant scoliosis, the convexity being to the left. There was no definite evidence of osteomyelitis.

Autopsy.—Postmortem examination revealed gram-positive cocci in a staphylococcus formation in fresh vegetations on the aortic and mitral valves. There were miliary abscesses in the lungs, liver, kidneys, spleen, colon and skin, and a recent purulent prostatitis. The body of the fourth thoracic vertebra showed suppuration in its right lateral portion. There was suppuration in the surrounding paravertebral structures and in and about the fourth right costovertebral articulation. No perforation was seen leading from the body of the fourth thoracic vertebra into the epidural space. An extensive epidural abscess was found, apparently secondary to the suppuration in and about the fourth right costovertebral articulation. On October 15, from the epidural abscess yielded Staphylococcus aureus on culture. On October 17, vegetations from the aortic and mitral valves showed gram-positive cocci in staphylococcus formation.

Comment.—This patient had an acute bacterial endocarditis, most probably secondary to squeezing a furuncle of the neck, with multiple

metastatic abscesses, one of which was situated in the fourth thoracic vertebra and gave rise to an epidural abscess. Of interest is the following consideration:

It is possible that the localization of bacteria occurred in the body of the fourth thoracic vertebra because of the existence of an old lesion of this bone, as evidenced by the x-ray plate and the sclerosed bone removed at operation, which had given rise to the scoliosis and possibly created a "locus minoris resistentiae."

CASE 16.—A. S., a man, aged 30, was admitted to the hospital on May 30, 1927, with a known history of Hodgkin's disease for two years, for which he had received roentgenotherapy with considerable relief. For two months he had been having increasing weakness and loss of weight with occasional fever. He had difficulty in breathing, and an intranasal operation was performed with some relief. There was also difficulty on urination.

Physical examination showed a markedly emaciated man *in extremis*. No lymph nodes were palpable. Murmurs were heard over the mitral and aortic areas. There was edema of the lower extremities, with evidence of fluid in the peritoneal and pleural cavities.

Course.—The patient died the day after admission, presumably with respiratory paralysis.

Autopsy.—Postmortem examination revealed a man with marked brownish pigmentation of the abdominal skin, edema of both legs, bilateral purulent bronchitis and bilateral pleural empyema. There were widespread Hodgkin's infiltrations in the lungs, liver, spleen, bone and retroperitoneal lymph nodes. There was 2,400 cc. of purulent fluid in the abdomen, secondary, probably, to multiple abscesses in the spleen. The lumbar vertebrae presented red marrow diffusely mottled by a yellowish translucent gray amorphous material. The fourth lumbar vertebra on section showed a broken-down area, the size of a cherry, filled with greenish pus. No bacteriologic studies were made.

Comment.—This case is one of widespread granulomatous disease with resulting cachexia. The widespread superimposed infection which probably arose from the purulent bronchitis, affecting especially the areas of Hodgkin's infiltrations, masked the presence of an abscess in a lumbar vertebra. In this case the latter was clinically insignificant.

ADDENDUM

Since the submission of this paper, two additional patients with vertebral osteomyelitis have been admitted to the hospital. One, a girl aged 14 years, suffered a metastatic infection of the fourth lumbar vertebra, secondary to a Staphylococcus aureus bacteremia following the squeezing of a boil. Roentgenograms of the spine taken one month after the onset of the disease showed no abnormality; one month later there was narrowing of the intervertebral space between the third and fourth lumbar vertebrae; after another month there was a kyphosis due to destruction and collapse of the fourth lumbar vertebra with almost complete disappearance of the intervertebral space between the

third and fourth lumbar vertebrae and haziness of the intervertebral space between the fourth and fifth lumbar vertebrae.

The other patient, a man of 37, had a Bacillus proteus infection of the urinary tract with Bacillus proteus bacteremia and metastatic infection of the sixth cervical vertebra. Roentgenograms taken about three weeks after the onset of the disease showed narrowing of the intervertebral space between the fifth and sixth cervical vertebrae; five weeks later, roentgenograms showed destruction and collapse of the sixth cervical vertebra.

In each of these cases, roentgenograms afforded evidence confirmatory of the clinical diagnosis of vertebral osteomyelitis. A point worth stressing is that in each case an intervertebral space adjoining the diseased vertebra was definitely narrowed before there was certain abnormality in the appearance of the diseased bone itself.

on the injured leg, the well leg being used for counter-traction. A plaster cast is applied on the well leg from the toes to the groin. To this a counter-traction stirrup is applied. On the injured side a pin is inserted through the tibia and attached to a stirrup. The injured leg is incased in a plaster cast which extends to the knee. The transverse lever that connects the traction and the counter-traction is then adjusted through a rod with a spring and turnscrew. A locknut at the end of the traction stirrup controls the rotation of the leg. The author claimed for this method ease in after-care, certainty of immobilization and greater comfort for the patient.

RESEARCH

Regeneration of the Hyaline Cartilage.—Santos [49] was able to demonstrate microscopically regeneration of hyaline cartilage in a series of femoral heads following complete intracapsular fracture. This occurred in the central area not covered by perichondrium as well as peripherally, and was often preceded by invasion and resorption of the dead cartilage by the subchondral bone marrow. The formation of new cartilage proceeded partially from the pannus covering the joint, but chiefly from proliferation of surviving hyaline cells, usually in the deeper layers of the cartilage.

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49. Santos, J. V.: Surg., Gynec. & Obst. **54**:650, 1932.

WOUND HEALING IN ANTERIOR GASTRO-ENTEROS-TOMY FOLLOWING VARIOUS METHODS OF SUTURE

AN EXPERIMENTAL STUDY IN DOGS

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Our primary object in this study was to ascertain whether serosal inclusions or cysts, such as are found not infrequently on the posterior parietal pelvic peritoneum, on the female pelvic viscera and elsewhere, would form on apposed serosal surfaces as in the case of gastro-intestinal anastomoses. As our work progressed, some of our observations were apparently so singular that we also became interested to know how wound healing following gastro-enterostomy progressed after the use of some of the suture methods most commonly practiced in this country and recommended by textbooks of surgery.

The latter generally advise one of three procedures for the closure of the so-called anterior ostial defect in gastro-enterostomy wounds: an ordinary continuous catgut suture [1] passed through the entire thickness of stomach and intestinal wall (fig. 2B) ; a Connell stitch [2] (fig. 1A), which is a continuous mattress suture that has its loop on the mucosal aspect of the stomach and intestine, or a so-called baseball stitch (fig. 1B) (Schmieden suture).[1b] It is noteworthy that some authors [3] recommend that, for the purpose of hemostasis, the *mucosa be turned*

1. (a) Da Costa, J. C.: Modern Surgery, Philadelphia, W. B. Saunders Company, 1925, pp. 1083 and 1085. (b) Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1929, vol. 6, chap. 6, pp. 47 and 84; chap. 12, pp. 32, 40, 46, 50 and 56. (c) Moynihan, B.: Abdominal Operations, ed. 3, Philadelphia, W. B. Saunders Company, 1918, vol. 1, p. 186; ed. 4, 1928, vol. 1, p. 396.

2. Da Costa (footnote 1). Lewis (footnote 1). Moynihan (footnote 1). Connell, M. E.: An Experimental Contribution Looking to an Improved Technique in Enterorrhaphy, Whereby the Number of Knots is Reduced to Two, or Even One, M. Rec. **42**:335, 1892.

3. Lewis (footnote 1). Moynihan (footnote 1).

outward and not inward when placing the first anterior row of gastro-enterostomy sutures, while others recommend that no effort be made to invert the free edges. Others are of the opinion that the type of suture method or the kind of suture material used probably makes little difference in the operative result. It is also common practice among some operators, who use clamps to hold stomach and intestine in place while doing a gastro-enterostomy, to excise the mucosa that everts from the cut anterior gastro-intestinal margins. This excision is done by some with the cautery. A consideration of the various other suture methods and the utilization of variously prepared suture materials as employed in this country would lead one far afield. However, the conclusion is inescapable that suture methods and materials as employed by some are unsatisfactory in the opinion of others, but an explanation is not forthcoming.

A review of the literature reveals astonishingly little experimental work on suture methods in an operative procedure so commonly and yet so variously performed. The observations of Mall,[4] while concerned only with the study of healing of intestinal anastomoses, are so fundamental and in some respects so pertinent to this study that they will be referred to later. Flint's [5] excellent paper is the only one that we have been able to find in the English language that concerns itself with a histologic study of wound healing in gastro-intestinal anastomoses. Flint's work was done on dogs, and his histologic study is most detailed. Anterior gastro-enterostomies were performed by one of three suture methods: (1) a two tier method employing interrupted silk sutures for each row; (2) a three tier method, the Wölfler technic, employing a continuous chromic catgut suture for the mucosa, a continuous silk or linen suture for the seromuscular layer and a serosal suture of interrupted silk or linen; (3) a two tier method consisting of an innermost continuous catgut suture and an outer layer of interrupted silk similar to our method 5. Flint found that the healing time following the use of these methods is approximately the same and that the mucosa is healed at about fourteen days, while at twenty-three days the mucosa over the operative defect is normal in places and the muscularis mucosae is partially regenerated.

Further reference to Flint's observations will be made later; however, his general conclusion is that, because of the incomplete mucosal healing before the fourteenth day following gastro-enterostomy it is of practical importance to keep the patients on a "light diet." It is also our impression that Flint's primary interest was more the study of wound healing than a determination of differences following various

4. Mall, F.: Healing of Intestinal Sutures, Johns Hopkins Hosp. Rep. **1**:76, 1896.

5. Flint, J. M.: The Healing of Gastrointestinal Anastomoses, Ann. Surg. **65**:202, 1917.

suture methods, for he did not mention the suture method employed when he described sections that showed certain unusual phenomena.

Gould [6] did not describe the suture technic employed in his experimental gastro-enterostomy studies, and one is not able to infer from his text whether there was a difference in healing following various methods of suturing. In general, the average time for mucosal healing was given as fourteen days. He stated [7] that on the tenth day a single line of cells starts across *from the stomach* and rapidly crosses the floor of the ulcer (the mucosal defect at the site of anastomosis).

The next histologic study that we encountered was by Gara.[8] In his experiments rabbits' stomachs were sectioned and then sutured by one of three methods: (1) a two tier method probably similar to our method 5; (2) a three tier method similar to our method 6, and (3) a method of his own which everts the sectioned tissues with the object of protecting the edges of the wound from the action of gastric juice. He claimed the best results with his method in that mucosal healing occurred in from one to two days. The three tier method, he stated, produces a smaller defect than the two tier method, but with both, contrary to our findings, he found mucosal healing incomplete in twenty-one days. Gara's report is inconclusive in that he described neither the suture material, the type of stitch nor the number of animals used in his experiments.

Klose and Rosenbaum-Canné [9] studied healing of wounds made with the cautery or scalpel in the stomach of sixteen cats. The wounds were sutured anteriorly only by one of three suture methods: (1) a one row serosal suture similar to our method 4; (2) the two row method of Czerny, and (3) the anterior inverting suture of Schmieden similar to our method 3. They killed their animals ten, twenty and thirty days after operation and found complete epithelization by the tenth day, following the use of the Schmieden suture. Epithelization was not complete after twenty days following the one row serosal suture method. The authors felt, however, that a two layer suture technic produces greater damage to the underlying structures than a single layer suture method; that cautery section produces much more inflammation and delayed union than knife section, and that although

6. Gould, A. H.: The Technic of Operations upon the Intestine and Stomach, Philadelphia, W. B. Saunders Company, 1906.

7. Gould (footnote 6, p. 23).

8. Gara, Max: Der Einfluss der Nahtmethode auf die Heilung operativer Kontinuitätstrennungen der Magenwand zugleich ein Beitrag zur Frage des Ulcus Pepticum jejuni postoperativum, Arch. f. klin. Chir. **120**:270, 1922.

9. Klose, H., and Rosenbaum-Canné, P.: Beiträge zur Magenchirurgie: I. Vergleichendexperimentelle Untersuchungen über die Magennähte. Arch. f. klin. Chir. **124**:15, 1923.

catgut as an inner row suture is absorbed, it produces considerable inflammatory change along the line of union as well as *marginal epithelial cysts*.

Kopyloff [10] studied gastro-enterostomy wound healing in sixty-one dogs following the use of five suture methods and the employment of various suture materials. He made observations also on the comparative rate of healing following scalpel, scissor and cautery incision, but did not study the comparative rate of healing following the use of various suture methods. He described, however, a ten day healing specimen from a gastro-enterostomy performed by means of a single layer of interrupted silk sutures (similar to our method 4) which showed epithelial union between the stomach and jejunum. The gastro-intestinal incision was made with a scalpel, and it was compared with another specimen in which a cautery was used and a mucous membrane defect was present after thirty days. He was in agreement with Klose and Rosenbaum-Canné that cautery incisions produce pronounced inflammation, thrombosis and delayed healing.

Kopyloff described "regenerative alveoli" in the mucosa at the margin of the previous operative defects as long as twelve months after operation. These are identical with the "marginal cysts" of Klose and Rosenbaum-Canné. He also described silk threads which migrated through the anastomatic site and lay in areas surrounded by epithelium that "resembles intestinal epithelium." These are identical with Mall's and our suture inclusions, and Kopyloff observed them in a three hundred and sixty-five day specimen. He did not describe mucosal inclusions in the line of apposition. Kopyloff, contrary to Klose and Rosenbaum-Canné, believes that the most rational method for gastro-enterostomy is a one layer serosal suture of fine catgut or interrupted silk (Lembert sutures) with a few interrupted catgut mucosal sutures at the angles of the anastomosis to maintain the size of the ostium. He unqualifiedly condemned continuous silk sutures and apparently was under the impression that all silk sutures eventually migrate into the gastro-intestinal lumen, while Lembert sutures migrate not through the line of apposition but at a point some distance from it. He gave no explanation for these phenomena, being evidently unaware of Halsted's fundamental studies [11] and the fact that his silk sutures migrate into the gastro-intestinal lumen because they are placed too deeply, piercing the mucosa.

10. Kopyloff, G.: Über das Schicksal der Magendarm-Anastomose bei verschiedenen Nahtmethoden und bei einigen Modifikationen in der Operationstechnik. Arch. f. klin. Chir. **136**:568, 1925.

11. Halsted, W. S.: Intestinal Anastomosis, Bull. Johns Hopkins Hosp. **2**:1, 1891. Circular Suture of the Intestine, Am. J. M. Sc. **94**:436, 1887.

Nemiloff [12] reported histologic studies on gastro-enterostomy wounds in eight patients who died two, three, six, twelve, fourteen and twenty-four days, and in one instance nine months, after operation. A three layer technic using continuous silk was employed. A mucosal defect was noted in all the specimens up to and including the twenty-four day preparation. The nine months healing preparation showed complete mucosal healing and a silk thread in the line of anastomosis surrounded by mucosal glands. Nemiloff also observed dilated glands in the mucosa where it bordered the operative defect. *Restitutio ad integrum* was not observed, for definite scar formation was found underlying the regenerated mucosa.

The report of Strauch [13] is the most recent experimental histologic study that we have seen. Strauch used twelve dogs and ran two series of experiments. In one he sectioned the stomach transversely, and in the other he did anterior gastro-enterostomies and occluded the pylorus. The cut edges in both series were reunited by using several suture methods on the same specimen. In all experiments catgut suture material was used, and the dogs were killed at intervals of from two to forty-four days. Several suture methods were used: posteriorly (*a*) a single layer serosubmucosal suture which left the mucosa unsutured; (*b*) a two layer suture, one a serosubmucosal suture and the other a through-and-through suture of all the coats; (*c*) a two layer suture, one layer embracing the serosubmucosal structures and the other merely a so-called mucosal stitch, and (*d*) a three layer suture just as in our three layer method 6. Anteriorly, Strauch used three suture methods; (*e*) a two layer method, the innermost being a baseball (Schmieden) stitch similar to our method 3; (*f*) the everting method of Gara, and (*g*) a two layer method, the innermost being a continuous suture (Kürschner) involving all the coats and similar to our method 5.

Strauch concluded that suture methods *b, c, d, e,* and *g,* showed no marked differences in wound healing. However, with method *a* he found marked delay in healing owing to gaping of the mucosa, and he believes that any technic which does not bring the mucosal surfaces together delays healing. Strauch believes that posteriorly method *b* or *c* and anteriorly method *e* or *g* are the most desirable procedures. He did not describe marginal mucosal cysts or any type of epithelial inclusions.

We believe that the small number of animals used and particularly the simultaneous employment of several suture methods on the same animal present real defects in Strauch's experimental procedure.

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12. Nemiloff, A.: Ueber den Heilungsprozess in der Gastroenterostomiewunde, Arch. f. klin. Chir. **135**:629, 1925.

13. Strauch, C. B.: Histologische Untersuchungen ueber den Einfluss der Nahttechnic bei Magenoperationen auf die Heilung, besonders der Schleimhaut, Arch. f. klin. Chir. **137**:81, 1925.

PLAN OF STUDY

Forty-two dogs were used in two series of experiments for this study, twenty-two animals being employed in the first series and twenty in the second. The first series was completed and the histologic material examined before the second series was begun in order that observations made on the second might either confirm or refute the observations of the first series as chance occurrences incidental to some uncontrolled technical pitfall. Two animals died of postoperative complications, one (dog 20) dying on the table as the result of the anesthetic and the other (dog 54) of an infection of the upper respiratory tract thirty-four days after operation. Three specimens, from dogs 15, 20 and 27, were not used for study, so that our observations are based on thirty-nine animals.

Either an anterior gastroduodenostomy or a gastrojejunostomy was performed on each animal under ether narcosis and with customary surgical asepsis by the suture methods to be described. Water was given the animals as soon as they would take it. On the fourth day after operation, the day of operation being counted as one, milk and hamburger steak were added to the ration; on the sixth day the ordinary kennel ration, milk and dried horse meat, was given. It is obvious that no attempt was made to shield the gastro-intestinal wound from contact with coarse food.

The animals were killed by chloroform, six, nine, fourteen, twenty and twenty-seven days after operation. An autopsy was immediately performed. The distal two thirds of the stomach and the anastomosed intestine were removed with as little manipulation as possible and placed in a fresh diluted solution of formaldehyde U. S. P. (1:10). The specimens were not disturbed until fixation was complete; then blocks were taken by razor section from the midportion of the anterior and posterior anastomatic areas. Paraffin embedding was employed, and the sections were stained with hematoxylin and eosin.

SUTURE METHODS

Seven different suture methods were employed in this study and will be referred to by number rather than by a descriptive appellation. The suture materials were the same throughout, 00 plain catgut and 0 black silk. The finest curved intestinal needles were employed. In all our experiments stay sutures of silk were used, and the first posterior suture was a continuous serosubmucosal stitch of silk. Also, in all our experiments, the final anterior tier of sutures were Halsted serosubmucosal mattress sutures of silk.

Method 1 (Connell suture) was used only on the anterior aspect of the ostium, and consisted of a continuous through-and-through mattress suture of catgut with its loop on the mucosal aspect of the stomach and intestine, as shown in figure 1 *A*. This suture inverts the mucosa readily and, as previously noted, is a method described in some of the surgical textbooks. It was reenforced by a second row of Halsted sutures as already mentioned.

Method 2 was used only posteriorly. After the first posterior tier of silk was placed, the stomach and intestine were incised, and a second suture of continuous catgut was placed as a through-and-through lock-stitch or button-hole suture embracing the entire thickness of both walls. This suture was not used anteriorly because it formed (dog 15) a ridge of tissue so large as almost to prevent its peritonization by a second row of Halsted sutures.

Method 3 was used only on the anterior aspect of the gastro-intestinal ostium. It consisted of a continuous catgut suture passed from side to side alternately, the suture always passing from mucosa to serosa—a so-called baseball stitch (fig. 1 *B*).

This suture method, macroscopically at least, inverts the mucosa satisfactorily, without technical difficulty, and is one commonly recommended in some American textbooks. This suture line was, in turn, peritonized by a serosubmucosal row of silk Halsted sutures.

Method 4 (the Halsted presection method[11]) was used anteriorly only and employed a single row of presection Halsted sutures of silk. Hemostasis on the anterior aspect of the ostium was effected with free ties of catgut. When the presection sutures were tied, those intervals between them which required it were sutured with Lembert or Halsted stitches of silk (fig. 2 A). This method gives most excellent and ready inversion of the mucosa and is described in American textbooks only for use with the Finney pyloroplasty.[15]

Method 5 was used both anteriorly and posteriorly. It was used posteriorly as a second tier continuous catgut suture that passed through all the coats of stomach and intestine after they had been incised, and served as an effective hemostatic
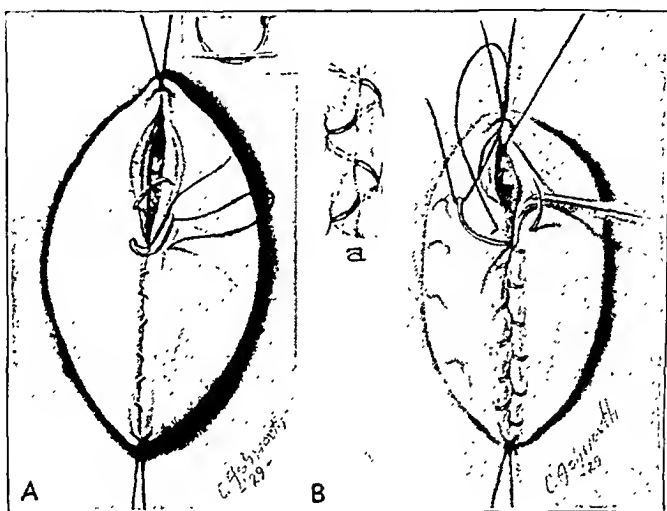
Fig. 1.—A, suture method 1, the Connell stitch, which is used only on the anterior aspect of the gastro-intestinal ostium. B, suture method 3, the so-called baseball stitch, which is used only on the anterior aspect of the gastro-intestinal ostium. Schematic illustration of suture is shown at a.

stitch. Anteriorly again it was used as a continuous catgut stitch that passed through all the coats of stomach and intestine and inevitably resulted in eversion of the mucosa and the formation of a ridge of tissue that at times was difficult to peritonize by the second tier of Halsted stitches. Figure 2 B illustrates this suture method, which is one strongly advocated and described in various textbooks of surgery.

Method 6 was employed both anteriorly and posteriorly. The first posterior tier of silk was placed as usual, and the stomach and intestine were incised down to the submucosa. A second suture of continuous catgut was then placed through

14. Halsted (footnote 11, first reference).

15. Finney, J. M. T.: A New Method of Pyloroplasty. Tr. Am. Surg. A. **20**: 165, 1902.

the serosa and muscularis of both stomach and intestine. Some submucosa was also included in this suture, care being used not to pierce the mucosa. The submucosa and mucosa were then incised and sutured with a third tier of continuous catgut. This last suture is often spoken of as a mucosal suture. However, mucosa will not withstand even the slightest suture tension, so that some submucosa must be included. The anterior sutures were then placed by continuing the third posterior row to form the first anterior row, which included only mucosa and submucosa. The second posterior row was continued to form the second anterior row of continuous stitches, which on the gastric side included muscularis and submucosa and on the intestinal side, owing to the thinness of the intestinal wall, muscularis and serosa. The third row of sutures was, as previously noted, of silk Halsted stitches. Figure 3 illustrates this method, which is one employed by numerous operators. It is effective for hemostasis and generally produces little mucosal eversion on the anterior aspect of the ostium.
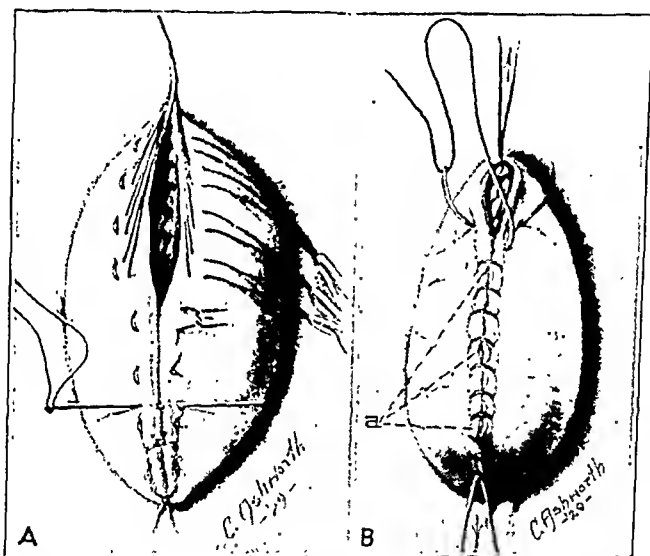
Fig. 2.—*A,* suture method 4, the Halsted presection suture technic, in which only one row of sutures is used on the anterior aspect of the ostium. *B,* suture method 5, an ordinary continuous suture, which is used both anteriorly and posteriorly. When used on the anterior aspect of the ostium, it inevitably causes macroscopic mucosal eversion, as shown at *a.*

Method 7 was employed both anteriorly and posteriorly in a third series of animals. In this report we shall describe only the results with the use of this suture posteriorly. The second posterior suture in this method is the same as that used for the second posterior row in method 6 (fig. 3). After being incised the mucosa was not sutured, hemostasis being effected by ligation of individual bleeding points.

This posterior suture is obviously ineffective for hemostasis. We were interested, however, in comparing the healing process following this suture method, which did not suture the two mucosae together, with the other posterior methods, viz., methods 2, 5 and 6, for it seemed to us that probably one of the sutures used in the three tier method was superfluous. The use of this suture on the anterior aspect of the ostium will be reported in another paper.

HEALING OF THE ANTERIOR ASPECT OF GASTRO-ENTEROSTOMY WOUNDS

Our primary interest in this study was the observation of wound healing. It was essential, therefore, that our specimens be obtained with the least possible manipulation at the time of autopsy and that undisturbed fixation be permitted before the specimens were cut. As a consequence, observations as to the size of the gastro-intestinal ostium had to be estimated on hardened tissue, and we therefore doubt their value. It can be said, however, that in so far as the diameter of the ostium was concerned, it measured 3 cm. in our smallest specimen and 6 cm. in our largest, the average being about 4 cm. In other words, even in the fixed specimens the ostia were adequate in size, but they
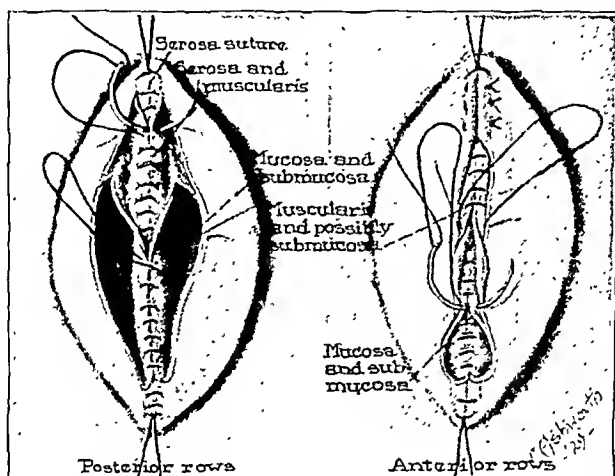
Fig. 3.—Suture method 6, a three layer method, which is used both anteriorly and posteriorly.

probably do not reflect in any accurate way the condition in vivo when one stops to consider the extensive and rapid change in size to which stomach and intestine are susceptible.

In preference to the foregoing, we measured the depth of the inner flange in the belief that this would give us some necessary information as to the comparative narrowing of the smallest ostial diameter caused by the various suture methods. These results will be summarized, as will our observations on the occurrence of adhesions. The following observations are confined to histologic detail and are here given only in briefest outline. No attempt is made to go into minute histologic description, for the meticulous descriptions of Mall and of Flint adequately portray the general process of the healing of intestinal and gastro-intestinal wounds.

METHOD 1 (Connell Suture).—Nine dogs (9, 11, 12, 13, 14, 32, 37, 42 and 47) were killed as follows: Two on the sixth day, two on the ninth day, two on the fourteenth day, two on the twentieth day and one on the twenty-seventh day.

Six day specimens (14 and 37) showed a well defined defect on the mucosal aspect at the point of stomach and intestinal apposition. Here there was a flat depression covered over by a fibrinocellular membrane, beneath which was a broad zone of young granulation tissue that extended into the submucosa for a short distance. Beyond this, where the serosal aspect of stomach and intestine had been apposed, one saw a broad zone of fibrous stroma with some round and polymorphonuclear cell infiltration and some capillaries. About the catgut sutures in the intestinal wall was a compact polymorphonuclear cell infiltration which was actually an abscess that extended out to the mucosa. Here the intestinal glands showed characteristic dilation and distortion due to the suture trauma.

On the gastric side also was seen mucosal gland distortion and nuclear pyknosis where the catgut had pierced its substance, but here there was much less cellular infiltration.

On the gastric side of the mucosal defect were seen a few dilated glands which we have termed marginal cysts. These, as will be seen, were rather characteristic of the reaction of gastric and intestinal mucosa to trauma. The gastric mucosa showed varying degrees of cellular infiltration and edema up to and slightly beyond the point of the catgut suture defect. Parietal cells extended to within eight to ten gland-breadths of the mucosal defect.

On the intestinal side the tips of the villi showed the most outstanding evidence of injury. In many areas they had undergone complete degeneration. Others showed only partial degeneration with marked enlargement and cellular infiltration. This often extended well beyond the area of suture injury. The advancing epithelial margin of the mucosal defect on the intestinal side showed at times a layer from 2 to 3 cells thick; again one saw a single layer of cuboidal epithelium which became low cuboidal or flat in the most advanced 2 or 3 cells. Secretion globules were seen in some of these cells almost up to the most terminal cell of the advancing margin.

No serosa cells were seen in the line of apposition. The muscularis mucosae showed considerable distortion for a short distance from the mucosal defect. The muscularis on both sides showed marked distortion, with some cellular infiltration for the entire extent of the apposed area. Here and there some degeneration was seen.

The silk sutures showed well defined fraying and were embedded in a loose matrix of short spindle-shaped cells with a few large round cells. Some sutures had a moderate polymorphonuclear cell infiltration about them, while others showed no cellular type of reaction. The serosa proper showed a moderate granulation tissue reaction.

Nine day specimens (9 and 32) still showed a well defined, though smaller, mucosal defect covered by a pyogenic membrane. There was excellent fibrous union along the line of apposition, and probably there was less cellular infiltration than in the six day preparation. The specimen from dog 32 showed a well defined mucosal inclusion (fig. 4) near the serosa on the intestinal side of the anastomosis. This was lined by columnar epithelium with oval, basally situated nuclei; secretion globules were common. These and other inclusions will be discussed later.

Fourteen day specimens (11 and 42) showed a moderate mucosal defect in dog 11, while in dog 42 epithelium covered the site of apposition of stomach and intestine (fig. 5). Here there was incipient gland formation. Elsewhere along

the line of apposition out to the serosa there were varying degrees of cellular infiltration, most marked in dog 11, through a zone of compact fibrous stroma.

Twenty day specimens (12 and 47) showed a moderate mucosal defect in dog 12, while in dog 47 mucosal union was complete and showed gland formation. In both specimens there were varying degrees of cellular infiltration in the line of apposition. In some sections from dog 12 there was some hemorrhage which had separated histologically the two infolded surfaces.

A twenty-seven day specimen (13) showed mucosal union complete without gland formation. Union along the inner three fourths of the line of apposition

Fig. 4.—Dog 32, anterior method 1, nine day healing: *a*, site of mucosal defect with a granulation tissue mound; *b*, marginal cyst on the gastric side of the mucosal defect; *c*, suture inclusion near the serosal aspect on the intestinal side of the line of apposition; *I*, intestinal mucosa; *S*, gastric mucosa.

was rather loose, and varying degrees of cellular infiltration existed. There was no fresh granulation tissue. Healing near the serosal aspect was firm.

Summary.—The outstanding observations following the use of the Connell suture were the persistence of evidence of active inflammation in the line of apposition up to twenty-seven days after operation and also, in one specimen, evidence of hemorrhage and loose union. Mucosal healing occurred first at

fourteen days, and a mucosal inclusion in the wall of the intestine was observed once. In general, appositional healing appeared firm.

Method 3 (Baseball Stitch, Schmieden Suture).—Seven dogs (16, 17, 18, 19, 34, 38 and 43) were used and were killed as follows: two on the sixth day, two on the ninth day, two on the fourteenth day and one on the twentieth day. Six day specimens (16 and 34) showed a well defined mucosal defect (fig. 6), a pronounced cellular infiltration from mucosal to serosal aspects and well developed compact granulation tissue along the line of apposition. Nine day specimens (17
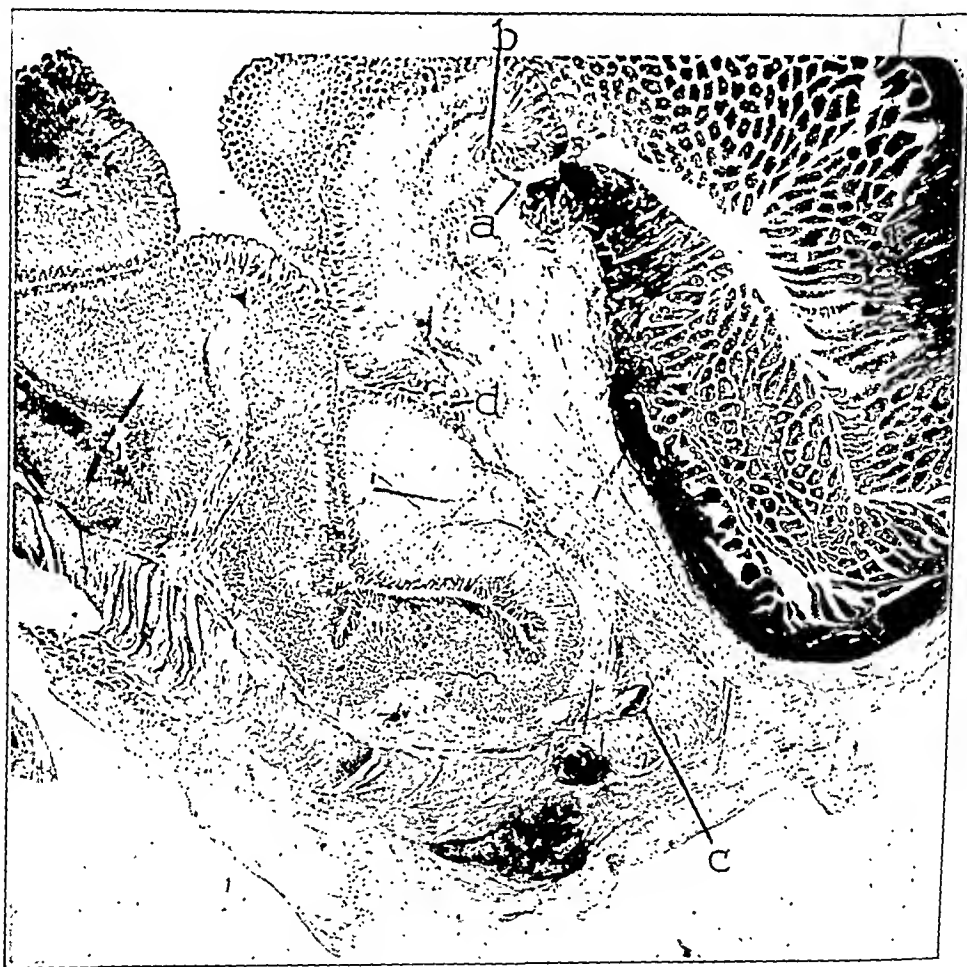
Fig. 5.—Dog 42, anterior method 1, fourteen day healing: *a*, site of the mucosal defect covered with a single layer of columnar epithelium; *b*, marginal cysts on the gastric side of the previous mucosal defect; *c*, silk sutures in the wall of the stomach; *d*, place where the catgut suture pierced the wall of the stomach. Excellent healing along the line of apposition.

and 38) showed mucosal union complete without gland formation in dog 17, while dog 38 had a well defined defect. There was a marked cellular infiltration from mucosal to serosal aspects, and a compact zone of young fibroblasts occupied the line of apposition. Fourteen day specimens (18 and 43) both showed complete mucosal healing with gland formation and little evidence of inflammation at the

site of union. Mucosal inclusions were seen in the line of apposition in both specimens. This was especially marked in dog 43, as is shown in figure 7. This inclusion resembled intestinal mucosa in that its epithelium, containing mucous globules, was columnar, with coarsely granular basal nuclei, and had the tinctorial properties of the intestinal mucosa. The glands were tubular with a cellular interglandular stroma, and there was some exudate in the lumen of the inclusion. These inclusions in the line of gastro-intestinal apposition have been previously described by us.[16] and will be considered more fully later in this paper. A twenty day specimen (19) showed complete mucosal union without gland formation and
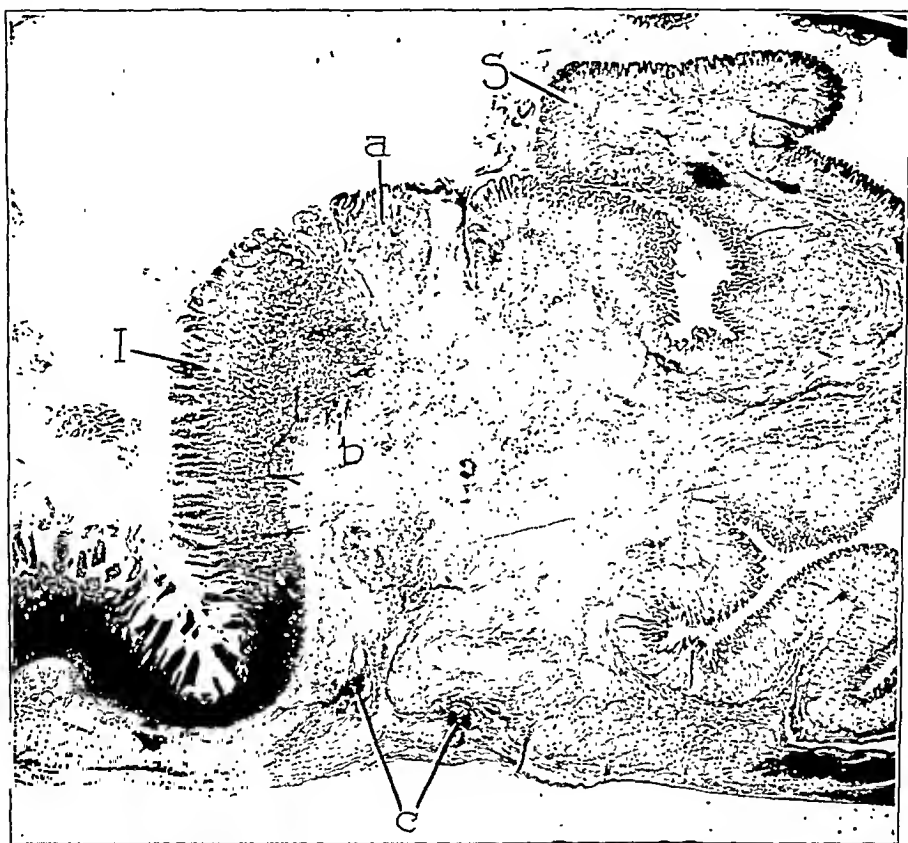
Fig. 6.—Dog 34, anterior method 3, six day healing: *a*, plateau-like granulation tissue material covered by a fibrinocellular membrane at the site of the operative mucosal defect; *b*, dilated intestinal glands, indicating place where the through-and-through catgut suture pierced the intestinal wall; *c*, silk sutures showing some fraying, a moderate round cell infiltration and a well defined surrounding hyaline change. Pronounced acute inflammatory reaction in the line of apposition. *I*, intestinal mucosa. *S*, gastric mucosa.

16. Martzloff, K. H., and Suckow, G. R.: Mucosal Inclusions in Anterior Gastroenterostomies in Dogs Following Various Methods of Suturing, Proc. Soc. Exper. Biol. & Med. **27**:855, 1930.

a mucosal inclusion in the line of apposition. Otherwise there was good fibrous union, with little evidence of cellular infiltration.

Summary.—Most of these histologic preparations showed considerable inflammatory change, not described in the individual protocols, in the mucosa of the stomach and intestine at some distance (from 0.5 to 1 cm.) from the line of apposition. Usually mucosal deformities could be seen which indicated the place where a catgut suture had pierced the viscus wall. Inflammatory cell infiltration was marked at the site of anastomosis in all specimens up to and including the nine day preparations. One of four specimens obtained with six and nine day healing showed mucosal continuity reestablished over the site of anastomosis. *Mucosal inclusions in the line of apposition* occurred in three of the seven specimens. The
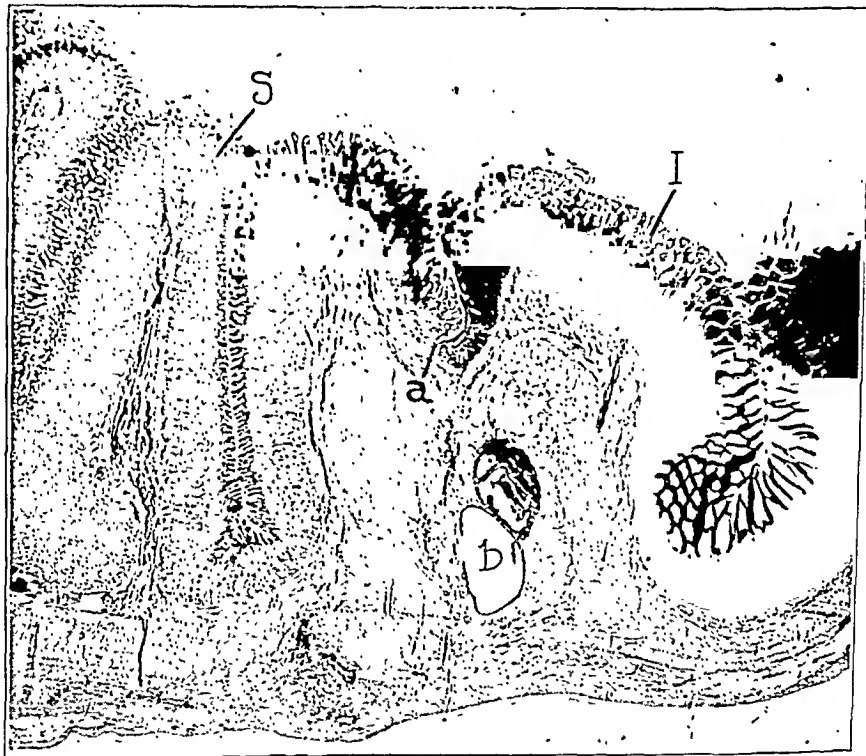
Fig. 7.—Dog 43, method 3, fourteen day healing: *a,* site of gastro-intestinal mucosal regeneration; *b,* mucosal inclusions (appositional rests) in line of apposition. The inclusion above *b* resembles intestinal mucosa. The mucosal epithelium is columnar; the nuclei are pyknotic and basally situated; many of the cells are distended with secretion globules. Inclusion *b* apparently shows evidence of distention, in that its walls are smooth and its lining epithelium is low cuboidal. There is well defined cellular infiltration along the line of apposition. *I,* intestinal mucosa. *S,* gastric mucosa.

healing of the mucosa and along the line of apposition in this suture method therefore surpasses that occurring in method 1. On the other hand, this method shows a high incidence of appositional mucosal inclusions.

METHOD 4 (Halsted Presection Sutures).—Seven dogs (21, 22, 23, 33, 39, 44 and 50) were used and were killed as follows: two on the sixth day, two on the ninth day, two on the fourteenth day and one on the twentieth day.

Six day specimens (21 and 33) showed complete mucosal union without gland formation (fig. 8) in dog 21, while in dog 33 healing was incomplete. Union along the line of apposition in dog 21 was remarkably free from cellular infiltration. There was a moderate granulation tissue structure beneath the mucosa, but elsewhere along the line of apposition no granulation tissue was seen, and there was very little round cell infiltration. In specimen 33 there was a well defined poly-
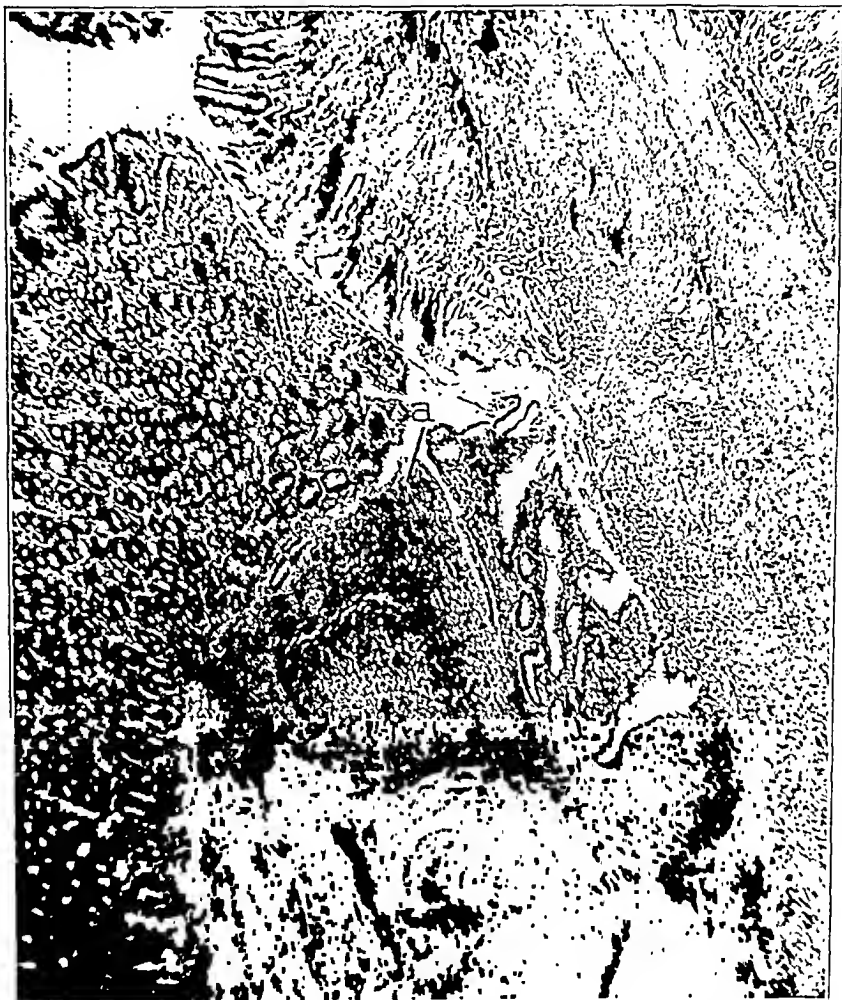
Fig. 8.—Dog 21, method 4, six day healing: a, site of operative damage to the mucosa, which is now covered with a single layer of columnar epithelium overlying an aggregation of round cells resembling a lymph follicle. Healing further out in the section, not shown here, is excellent, with a minimum of inflammatory reaction.

morphonuclear cellular infiltration at the mucosal defect, while further out in the line of apposition there were capillaries and fibroblasts with few accompanying round cells. Nine day specimens (39 and 50) showed complete mucosal union in

dog 50 (fig. 9), while a very small mucosal defect still persisted in dog 39. There was granulation tissue formation immediately beneath the mucosal defect in dog 39; otherwise both specimens showed very little cellular infiltration along the line of apposition. The healing in these two preparations was exceptionally free from evidence of inflammation and had the appearance of a firm union. Fourteen day specimens (22 and 44) showed complete mucosal union (fig. 10) with gland formation and a narrow, compact zone of fibrosis with practically no cellular infiltration along the line of apposition. These specimens showed the best fourteen day healing of any of our preparations. A twenty day specimen (23) showed complete mucosal and interstitial healing with practically no evidence of inflammatory reaction. The serosa over the anastomatic site appeared normal.
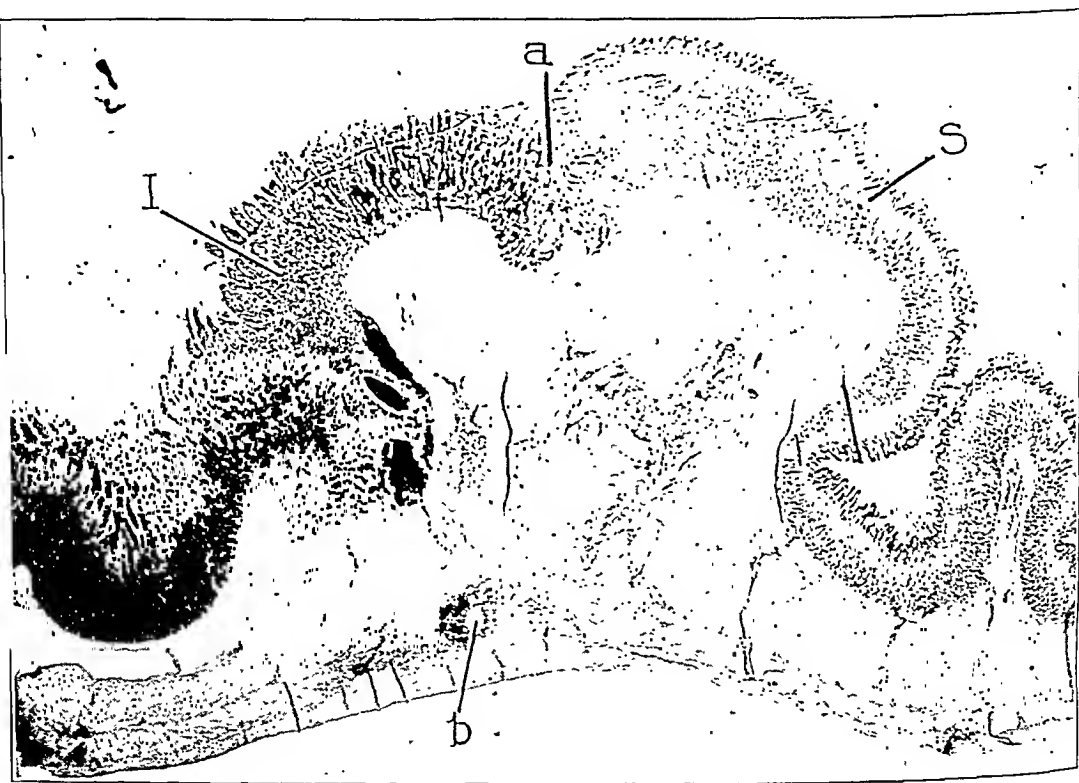
Fig. 9.—Dog 50, method 4, nine day healing: *a*, site of gastro-intestinal mucosal regeneration. Some loss of intestinal villi for a short distance to the left of *a*. Compact fibrosis along the line of apposition, with little round cell infiltration. Silk suture at *b*, to left of which there is an area of dense cellular infiltration, probably secondary to damage of the intestinal mucosa. Parietal cells of the stomach mucosa occur within from two to four gland-widths of regenerative defect. *I*, intestinal mucosa. *S*, gastric mucosa.

Summary.—Four of the six specimens obtained between the sixth and fourteenth days showed complete mucosal union. The specimens all showed remarkably little evidence of inflammation at the site of anastomosis, and no mucosal inclusions were seen.

METHOD 5 (Ordinary Continuous Suture).—Eight dogs (24, 25, 26, 35, 40, 45, 49 and 54) were employed and were killed as follows: two on the sixth day, one

on the ninth day, two on the fourteenth day, two on the twentieth day and one on the thirty-second day.

Six day specimens (24 and 35) showed most pronounced mucosal defects and an intense inflammatory reaction along the line of apposition. Large deposits of fibrinocellular material were present just beneath the serosa (dog 24), which strangely enough appeared virtually intact. In dog 35 (fig. 11) large open spaces, due to the dropping out of exudate, were seen in the line of apposition. Bits of mucosa were found well out in the line of apposition in dog 24. A nine day specimen (40) showed mucosal union incomplete, though only a small defect was
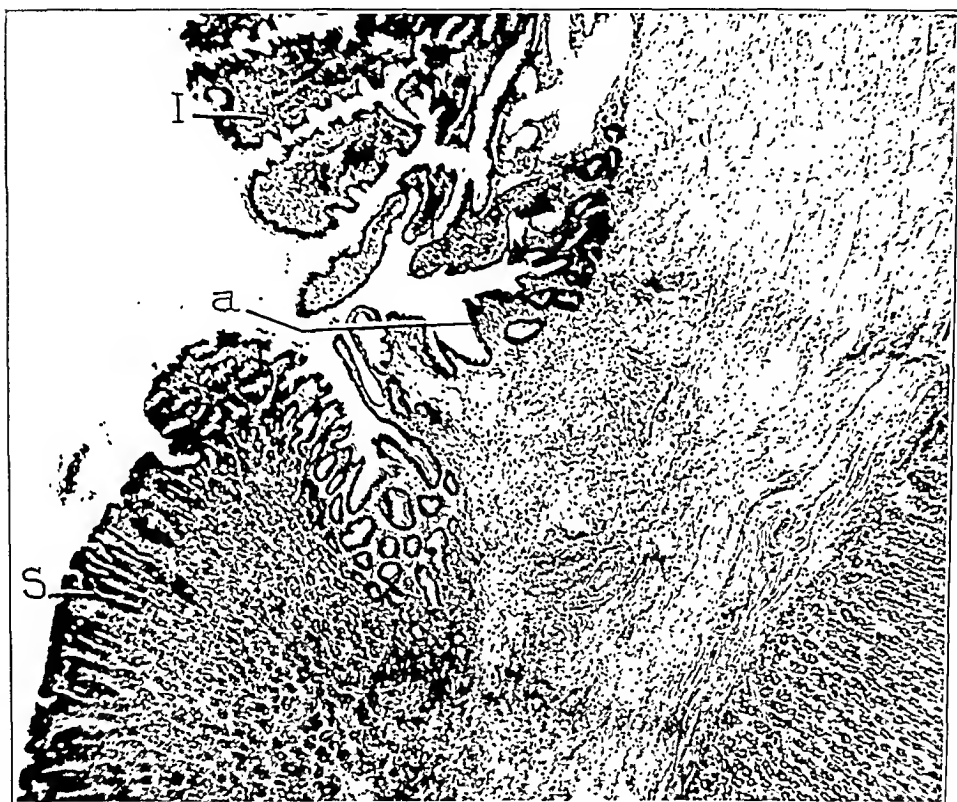
Fig. 10.—Dog 44, method 4, fourteen day healing. High power photomicrograph to show complete mucosal regeneration, with gland formation at *a*. The remainder of the section shows practically no inflammatory reaction along the line of apposition. *I*, intestinal mucosa. *S*, gastric mucosa.

left. There was a moderate degree of inflammatory reaction along the line of apposition, and here also a large *mucosal inclusion* was present. The latter, in some sections, was seen to communicate with the gastro-intestinal lumen. Fourteen day specimens (25 and 45) showed complete mucosal union with gland formation only in dog 45. Both had a well defined fibrosis and cellular infiltration along the line of apposition, while dog 25 showed a well defined mucosal defect covered with a fibrinocellular membrane. This same preparation showed a mucosal inclusion (fig. 12) extending well out in the line of apposition, while the specimen

from dog 45 showed a mucosal inclusion associated with a silk suture in the
intestinal wall. Twenty day specimens (26 and 49) showed mucosal union with
gland formation and mucosal inclusions associated with silk sutures on the intes-
tinal side of the preparation. In addition, preparation 49 (fig. 13) had a large
mucosal inclusion in the line of apposition, which we have previously reported.[16]
Both specimens showed considerable fibrosis and cellular infiltration in the line
of apposition. A thirty-second day specimen (54) showed a complete mucosal
union with gland formation at the line of anastomosis, but a few millimeters from
here there was extensive degeneration of the gastric mucosa. There was a large
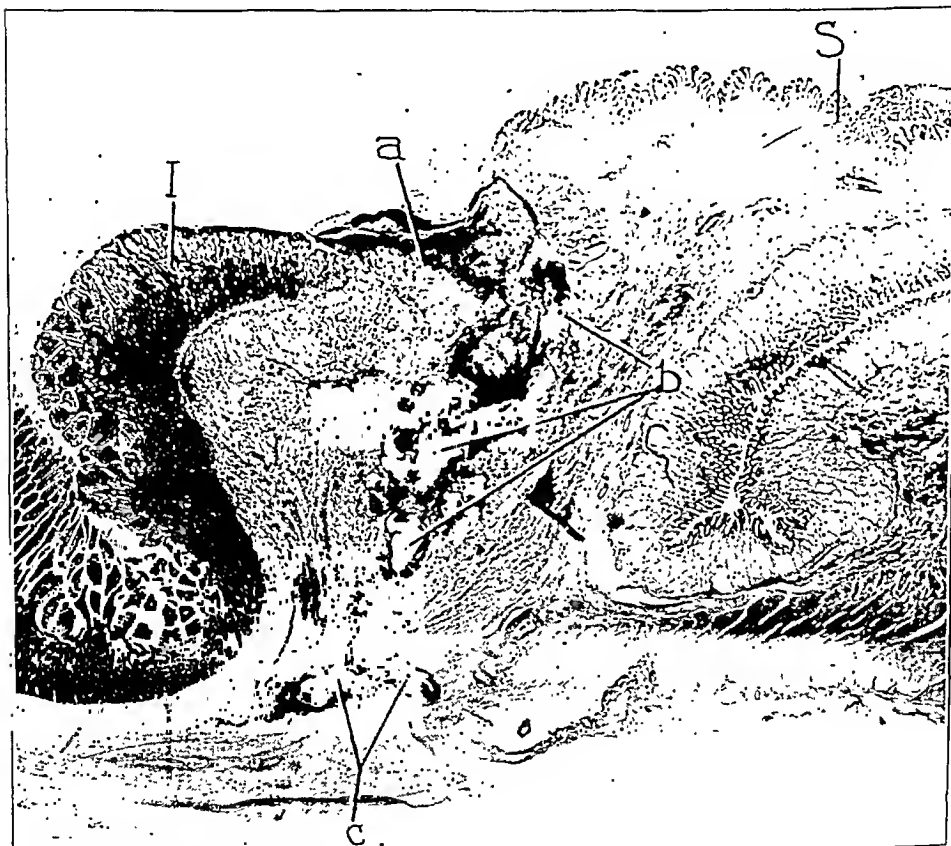
Fig. 11.—Dog 35, method 5, six day healing: *a*, broad granulation tissue
plateau covered with a fibrinocellular membrane occupying the zone of the opera-
tively produced mucosal defect; •*b*, large spaces from which the exudate has
dropped out. A profound inflammatory reaction in the line of apposition. Silk
suture defects are shown at *c*. *I*, intestinal mucosa. *S*, gastric mucosa.

mucosal inclusion, associated with a silk suture, that involved the intestinal
muscularis. The cyst was dilated and lined in part by a single layer of columnar
epithelium. This animal was not intended for inclusion in this series. However,
its premature death from pneumonia rendered it unsuitable for our third series,
so we included it in this report.

Summary.—Four of five animals operated on with this suture method and
killed on or before the fourteenth day showed incomplete healing of the mucosa.

As the specimens at each considerable evidence of active inflammatory reaction. There are practically free of the early healing period. Four of eight specimens showed punctured adhesions in the line of apposition, while a similar proportion showed mucosal adhesions are coated with silk sutures in the intestinal wall. One specimen contained both types of inclusions.

Fig. 12.—Dog 25, method 5, fourteen day healing: high power view from the mucosal aspect of a section showing mucosal inclusion in the line of apposition as *a*, which in some sections communicates with the gastro-intestinal lumen; *b*, a thrombosed blood vessel. This photomicrograph does not show a well defined mucosal defect with a pyogenic membrane that still persists.

Method 6 (Three Tier Suture Technic).—Eight dogs (28, 29, 30, 31, 36, 41, 46 and 48) were used for this method and were killed as follows: two on the sixth day, one on the ninth day, two on the fourteenth day, two on the twentieth day and one on the twenty-seventh day.

Six day specimens (28 and 36) showed large mucosal defects (fig. 14) with an overlying fibrinocellular membrane. There were marked cellular infiltration and a compact granulation tissue structure in the line of apposition. A nine day specimen (41) showed complete mucosal union in some sections (fig. 15), while others showed incomplete union. There were compact fibrosis and considerable cellular infiltration along the line of apposition, and here also a very small
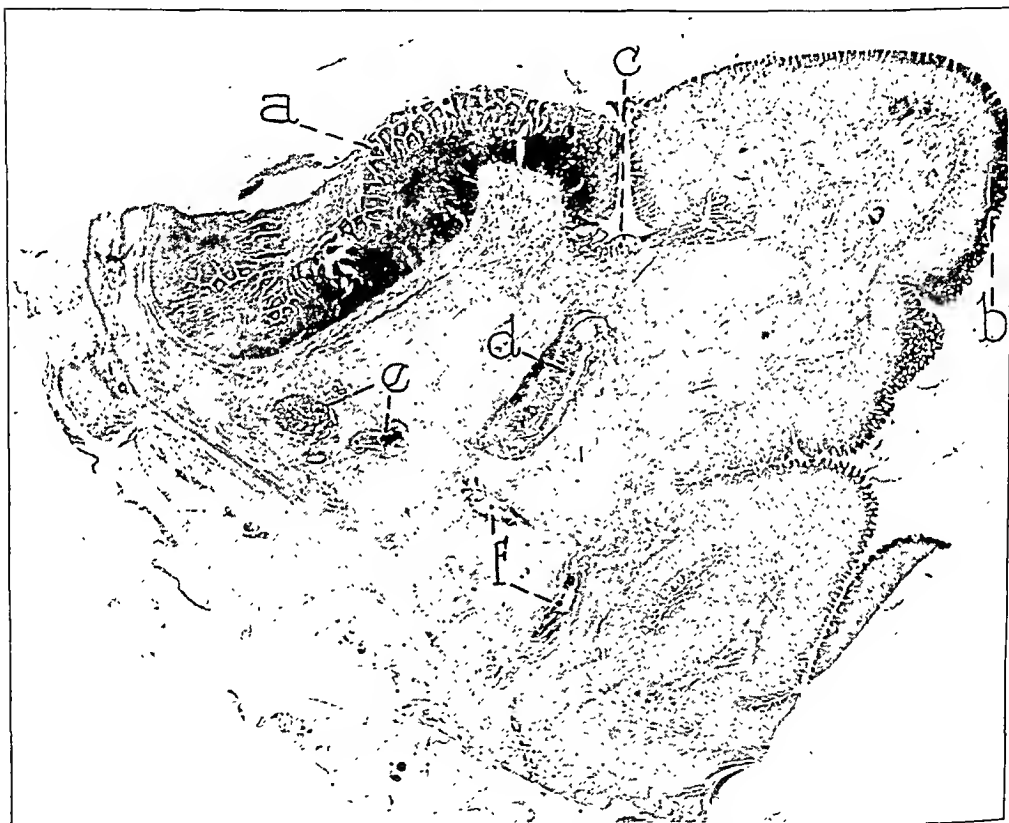
Fig. 13.—Dog 49, method 5, twenty day healing: *a*, intestinal mucosa; *b*, gastric mucosa; *c*, regenerated mucosal epithelium with gland formation at the site of a previous mucosal defect; *d*, appositional mucosal rest; *e*, suture inclusions on the intestinal side of the section, associated with a silk suture which lies in an epithelial lined space; *f*, silk suture defects.

mucosal inclusion was seen. Fourteen day specimens (29 and 46) showed mucosal union in the specimen from dog 46, while dog 29 still had a moderate defect covered with a fibrinocellular membrane. The line of apposition presented a compact fibrous structure with considerable cellular infiltration. There was a questionable mucosal inclusion in the line of apposition in specimen 29. Twenty day specimens (30 and 48) showed mucosal union with gland formation in specimen 48. In dog 30 there was so much round and polymorphonuclear cell

infiltration in the superficial one third of the intestinal mucosa that the gland pattern was almost wholly lost. There was a compact fibrosis along the line of apposition with moderate cellular infiltration in dog 48 and a more marked infiltration in dog 50, which also had a pronounced subserosal edema and round cell infiltration. A twenty-seven day specimen (31) showed mucosal union with gland formation over the line of anastomosis. This specimen also showed a pronounced inflammatory reaction involving the superficial portion of the gastro-intestinal epithelium.

Fig. 14.—Dog 28, method 6, seven day healing: *a*, mucosal defect with granulation tissue and an overlying pyogenic membrane; *b*, marginal cysts on the gastric side of the defect; *c*, area devoid of mucosa owing to a technical artefact. Compact granulation tissue union along the entire line of apposition with well defined peritonitis on the serosa. *I*, intestinal mucosa, *S*, gastric mucosa.

Summary.—Mucosal union occurred in one, and partially in another, of five animals killed on or before the fourteenth day. Mucosal inclusions were definitely observed in one specimen, but they were so small as to be of questionable significance. Inflammatory reaction in the line of apposition and in the mucosa was an outstanding observation in the preparations obtained following this suture technic.

General Considerations: Mucosa.—Marginal cyst formation is the term used to designate the dilated glands seen in the mucosa where it borders the site of the operative injury. These mucosal cysts (figs. 4, 5, 14 and 15) were first described by Mall, and since then have been observed and described by others.[17] They were frequently observed in our specimens irrespective of whether mucosal healing was complete

Fig. 15.—Dog 41, anterior method 6, nine day healing. This view is presented merely to show the excellent mucosal regeneration as a single layer of columnar cells without gland formation at *a* and marginal cysts at *b*. Other sections show incomplete mucosal healing. Further out in the section there is marked cellular infiltration in the line of apposition and a mucosal inclusion, which are not seen here.

17. Klose and Rosenbaum-Canné (footnote 9). Kopyloff (footnote 10) Nemiloff (footnote 12).

of incomplete. One of our specimens, to be described in another paper, showed marginal cysts after ninety days, and Kopyloff [10] observed them after twelve months. They were observed to occur on either the gastric or the intestinal side but most frequently on the former after any one of the suture methods that we have described. Since they occur after suture method 4, they are not necessarily due to suture trauma, as claimed by some. Their cause has not been definitely proved; however, since they are generally lined by a single layer of flattened epithelium and have not been observed by us to communicate with the gastro-intestinal lumen, we believe that they are probably traumatic occlusions or retention cysts. Mall expressed the opinion that while these cysts are in part made up of remnants of crypts, they are mostly new-formed.

Mucosal Epithelial Regeneration: All our preparations were not suitable for the study of the advancing margin of the regenerating mucosal epithelium. Some sections, because of their size, were too thick to permit reliable interpretation, while others showed evidence of disturbance of the pyogenic membrane, which ordinarily covers the granulation tissue that bridges the mucosal defects.

Numerous sections, however, were suitable for the observation of the advancing epithelial margin over the mucosal defect at the site of the operative injury, and we present our observations for what they may be worth. In some specimens epithelium was observed growing over a granulation tissue matrix and beneath a fibrinocellular exudate, and in others it was seen to advance over a granulating surface free from exudate up to the point where the epithelium stopped. Epithelial regeneration appeared to come from the intestinal side as much as from the gastric side, and in this respect our observations are not in conformity with Gould's.[6]

Some specimens showed in the terminal 2 to 3 mm. of epithelium an abrupt tinctorial and morphologic change. This consisted in the newer cells becoming lower and broader and taking a lighter stain. Generally the cell outlines for a distance of from 1 to 3 mm. from the advancing margin were indistinct, and no evidence of secretory activity was seen. However, in one of our preparations evidence of secretory activity (intestinal) was seen right up to the point where epithelial proliferation ceases.

The advancing epithelial membranes were sometimes composed of a single layer of flat, cuboidal or low columnar cells in which mitotic figures were almost never observed. In some specimens (fig. 16) the advancing edge were from 2 to 3 cells high, while the individual cells were round and not flattened. We have also seen all the foregoing, except the columnar cells, under a pyogenic membrane. One of our

specimens (fig. 17) showed a distinct single layer of columnar epithelium on the intestinal side extending up to the epithelial margin where it began to go under a pyogenic membrane. This same specimen showed on the gastric side a single layer of flat epithelium growing beneath a pyogenic membrane.

It would seem, therefore, that, in so far as our observations are concerned, regenerating gastric or duodenal epithelium may assume a varied morphology.
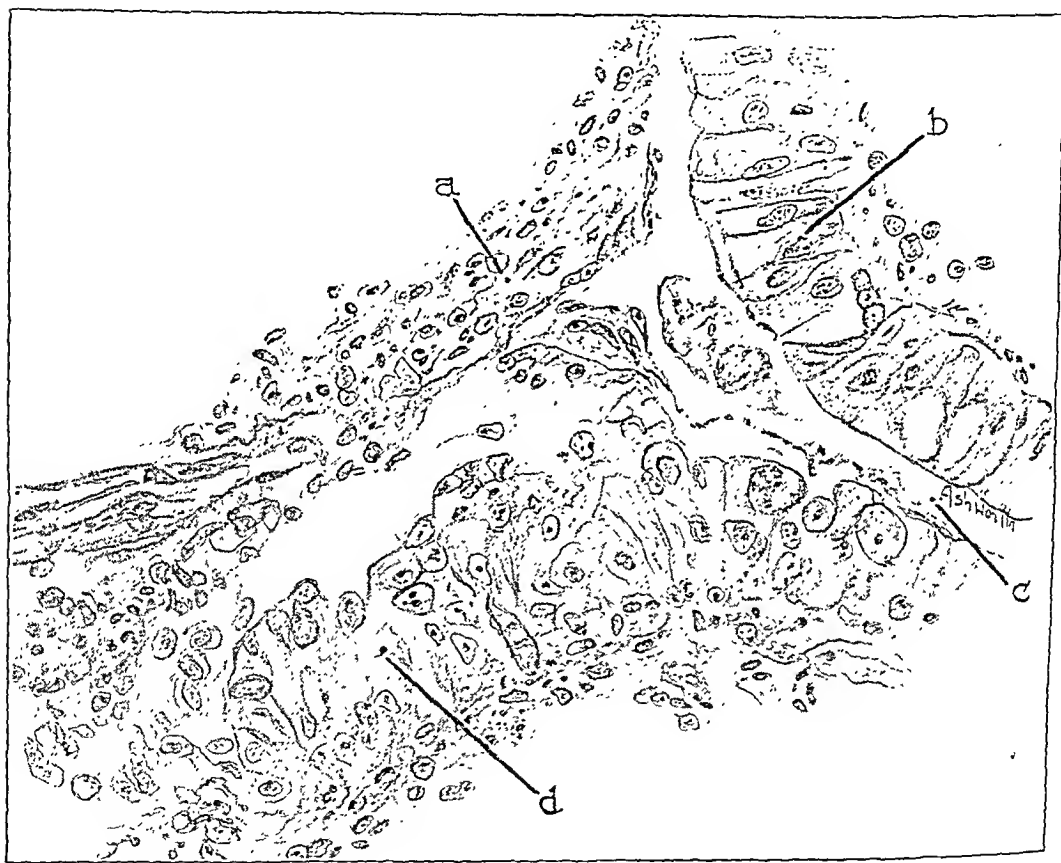
Fig. 16.—Dog 25. This drawing shows the advancing epithelial margin from the intestinal side at *d*, where the cells are several layers thick and round and oval in shape without any tendency to flatten, up to the point where they pass under a fibrinocellular membrane continuous with *a*. More or less normal intestinal epithelium is shown at *b*, and a crypt at *c*.

Gland Formation.—Gland formation in the mucosa covering the operative defect was not seen before the fourteenth day in any of our specimens. In the material from method 6 (three tier suture), gland formation in the area of repair was first observed in one specimen on the twentieth day. Although some specimens from all the other suture

methods employed showed gland formation on the fourteenth day of healing, it does not follow that all specimens with healing periods of twenty, twenty-seven or even thirty-two days, in which the same suture method was employed, showed gland formation in the area of repair. Gland formation as found in our material and also as observed by others appeared in its earliest stage as a mere dipping in of the epithelium into the underlying granulation tissue stroma.

Muscularis Mucosae, Submucosa and Muscularis.—The submucosa and the muscularis mucosae lose their identity entirely in the line of

Fig. 17.—Dog. 9. Intestinal epithelial margin advancing as a single layer of cuboidal or low columnar cells (*b*) which retain their shape as they pass under a fibrino-red corpuscular area (*c*). The most distal cells have unrecognizable cell membranes. In some sections it appears as if the most advanced epithelial cells have secretion globules. At *a* are shown young fibrous stroma and at *d*, mononuclear leukocytes.

apposition because of the inflammatory process in the early stages of healing and because of scar tissue in the later stages. The longest period of healing observed in this study was thirty-two days.

The muscularis retains its identity during the entire healing process, but by no means does it remain intact. In the early days of healing, the involvement of its outermost layers in edema and cellular infiltration varies considerably with the suture technic used. Later the muscle fibers of stomach and intestine are joined by fibrous stroma, which was

not spanned by muscle fiber during the period of healing here observed. In other words no *restitutio ad integrum* was seen.

Serosa.—The serosal surfaces where they came in contact through the apposition of the stomach and intestinal walls lost their identity in all our specimens. Our observations do not permit an opinion as to how early the serosal cells lose their identifiability. However, we believe that our material shows that no recognizable serosal inclusions occur at the point where two comparatively broad serous surfaces are apposed.
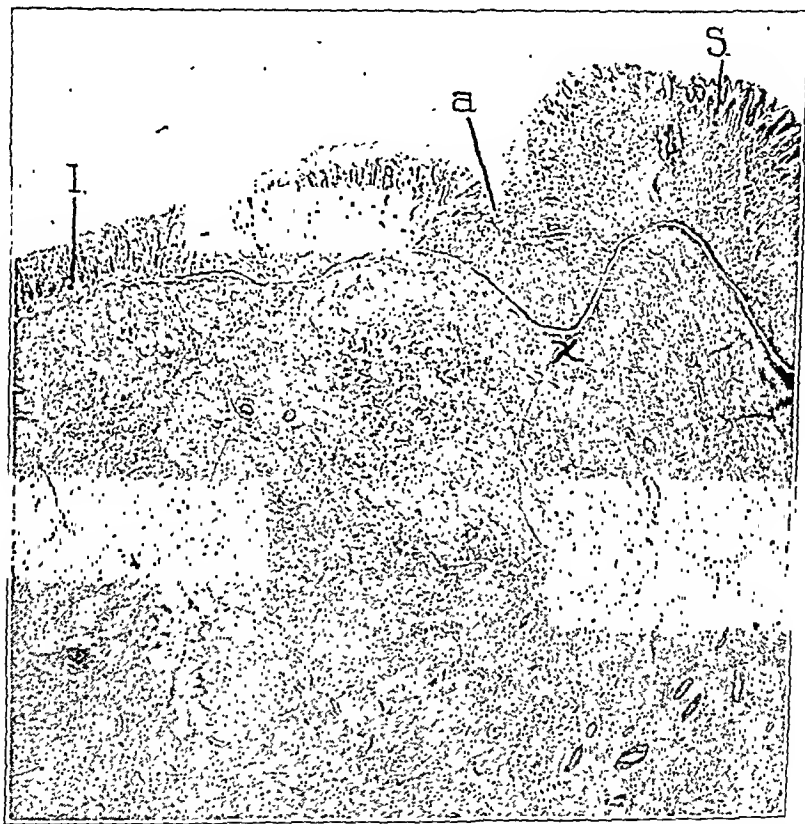
Fig. 18.—Dog 64, posterior method 7, six day healing. Remarkable mucosal restitution is shown at *a*, which extends to the line *x* drawn to show the boundary between the mucosa and the underlying stroma. Mucosa in area *a* shows distinct histologic alteration and does not resemble either intestinal (*I*) or gastric (*S*) mucosa. To the left of *a* is recognizable but altered intestinal mucosa with some dilated glands suggestive of marginal cyst formation. Healing further out in the section shows excellent fibrosis and little cellular infiltration.

This determination, among others, was one that this study was supposed to elucidate. Furthermore, we believe that the mucosal inclusions described by us in the line of apposition need not be confused with serosal cysts.

Mucosal Rests or Inclusions.—Reference to the illustrations and the brief protocols disclose that some of our specimens presented mucosal structures occupying one of two situations in the operative area; viz., (1) those found on the intestinal side of the anastomosis, generally in the intestinal wall nearer the serosa than the gastro-intestinal mucosal defect, and always associated with a silk ligature. These we have termed suture inclusions in contradistinction to (2) the mucosal rests which we found in the line of apposition between the walls of the stomach and intestine. These, for purposes of brevity, we have termed appositional rests.

Suture inclusions were observed in five specimens (figs. 4 and 13). Four of these were in animals in which suture technic 5 was used and the remaining one occurred with technic 1 (Connell suture). These inclusions, as shown in the illustrations, are all on the intestinal side of the anastomosis and are all associated with silk suture material. They may present a very simple gland structure, as in figure 4, or a more complex arrangement, as in figure 13. They are lined by a single layer of columnar epithelium which in places shows evidence of secretory activity, while mitotic figures are present. Their lumina generally contain a débris rich in polymorphonuclear cells, and there is considerable round and polymorphonuclear cell infiltration about the inclusions. In some preparations one can see evidence of damage to the intestinal wall near an inclusion that we interpret as being due to the inadvertent insertion of a silk suture into the mucosa at the time of operation. Due to pressure necrosis the suture cut its way through the mucosa, submucosa and a varying thickness of the muscularis, creating a defect along which the intestinal epithelium grew to form inclusions. These, therefore, are outgrowths which, in some specimens at least, communicate with the intestinal lumen to form small epithelial lined diverticula or sinuses. The evidence for this we shall present in another paper. In any event, these intramural glandular structures do not, as a rule, represent free grafts due to the transfer and implantation of isolated epithelial elements into the intestinal wall. The ultimate fate of these inclusions we do not know, but there is reason to believe [10] that they may persist indefinitely.

At first sight it may seem strange that such inclusions were encountered only in animals that were operated on by suture methods 1 and 5. The explanation is simple, in that with suture method 5 the tissues are so ridged at the line of apposition that it is difficult to place accurately the second row of silk Halsted mattress sutures. This results in an unintentional piercing of the intestinal mucosa in some specimens. Careless technic might easily produce the same formation in the other suture methods, which, however, afford conditions more suitable for the accurate placing of silk serosubmucosal sutures.

The nonoccurrence of analogous inclusions on the gastric side of the anastomosis is probably due to the greater thickness and toughness of the stomach submucosa, which thereby prevents the technical fault so easily committed on the intestine. Our experiments, however, do not definitely prove that gastric mucosa under similar circumstances would behave as the intestinal mucosa does. These inclusions have been observed by others [18] who, excepting Mall and Flint, gave them no consideration other than merely noting their presence. Mall,[4] however, is the first investigator to describe them and explain their origin as due to silk suture damage to the mucosal crypts. Mall also remarked that it is possible that these adenomatous structures "could do considerable mischief," but it appears that his original and beautifully accurate description, explanation and admonition have been largely overlooked.

Appositional rests, so-called, were observed eight times: in three specimens from suture method 3 (baseball stitch), in four specimens from suture method 5 (continuous stitch) and in one specimen from suture method 6 (three layer suture). Suture methods 1 and 4 were not complicated by these structures. It is noteworthy that these appositional rests occurred in methods in which sutures passed over free mucosal margins with resultant mucosal eversion. This fact is most marked with method 5. In method 6, eversion may also occur if the mucosubmucosal suture is not properly placed. Whether the catgut suture passing between the serous aspects of stomach and intestine in method 3 serves to act as a guide along which mucosa may grow, we cannot say. We have seen traces of catgut in the line of apposition in some of our six day specimens, but these were never associated with mucosal inclusions.

We do not believe that these appositional rests are due to mucosa growing along a zone of tissue damage produced by catgut as in the case of the so-called silk suture inclusions. If such were the case, laying aside all other considerations, one could expect to find some evidence of such a phenomena in suture method 1, in which sutures are passed directly through the entire thickness of stomach and intestine but without passing over the free inverted margin of either. It should be remembered that we are concerned here with 00 plain catgut suture material. These observations might not apply if a more durable variety of catgut were used. Some of our preparations showed areas of distinct damage to gastric and intestinal wall (including mucosa) by through-and-through catgut sutures, but in none of these did we see a suggestion of mucosal outgrowth along such a defect.

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18. Flint (footnote 5). Kopyloff (footnote 10). Nemiloff (footnote 12).

We believe, therefore, that the mucosal inclusions found in the line of apposition of our specimens arose from mucosal displacement following eversion and were not directly related to suture transfixion of the mucosa. The mucosa of these inclusions generally had the appearance of intestinal mucosa, but our specimens and observations did not explain the absence of gastric mucosa in these tests.

The only references that we can find regarding these appositional mucosal inclusions are by Marchand,[19] Gould and Flint. Marchand illustrated a six day gastro-enterostomy specimen of Professor Küster's which showed approximately in the line of apposition and near the mucosal aspect, a small adenomatous structure which he said was due to sutures (silk) passed through the mucosa which caused some infolding. It may well be that in this specimen the silk may have been the cause of a suture inclusion. Gould had one illustration in his book which may probably be construed as a form of appositional inclusion, but which he considered the site of a former ulcer between the two mucosae. Flint in his excellent paper noted that tearing of the muscularis mucosae or its failure to regenerate allows crypts of the intestine to grow into the submucosa. At times these growths, according to Flint, occur at the site of the incision and penetrate for some distance into the submucosa and muscularis.

It is evident that the significance of these adenomatous structures has not been recognized. Certainly they do not invade muscularis and submucosa, but are merely transposed so as to lie between their cut ends. If any invasion occurs, it is purely a secondary process and then only in the nature of a concentric physical displacement and not a heterotopia as seen in a malignant condition.

We are now studying the ultimate fate of these inclusions.

Fate of Suture Material.—Catgut: Some of our six day healing preparations showed catgut which appeared as a hyaline substance surrounded by polymorphonuclear neutrophilic leukocytes. No catgut was observed in any of our nine or fourteen day specimens. No conclusion could be made concerning its rôle in the production of inflammation, for it was contaminated in all methods by its passage through the gastro-intestinal lumen.

Silk: The reaction of the tissues to silk varied considerably in different specimens. In some early preparations the silk sutures showed some fraying and were surrounded by a slight to moderate round cell infiltration with or without an occasional polymorphonuclear leukocyte. The round cells were of two varieties, one being the easily recognizable lymphocyte and the other a large oval cell with a pink tinge to its nucleus.

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19. Marchand, F.: Der Process der Wundheilung, Stuttgart, Ferdinand Enke: Deutsche Chir. 1901, Pt. 16, pp. 300 and 306.

Some hyaline change was also observed in our six day healing specimens, while no giant cells were encountered in any of our material. In some of our older specimens as well as in an occasional six day specimen a hyaline reaction was about the only change noted about the silk sutures.

On the other hand, there were specimens both early and late in which every gradation from moderate cellular infiltration to frank abscess formation was seen about silk suture material. In fact some of the older preparations revealed practically no evidence of inflammation along the line of anastomosis until one arrived at a silk suture where a profound round and polymorphonuclear cell infiltration existed. These preparations generally showed evidence of damage to the intestinal mucosa where a suture was placed too deeply at the time of operation. Such findings were most common in suture method 5, and were not uncommon in the other suture methods except 3 and 4, in which they were also occasionally seen.

The explanation for these varied findings is probably merely a matter of surgical technic, and has been repeatedly stressed by Halsted. In preparations in which silk did not penetrate the mucosa, inflammatory reaction was minimal or virtually absent, while every degree of inflammation was observed when the mucosa was penetrated.

In suture methods 3 and 4, it was possible to place the Halsted silk mattress sutures so precisely that only occasionally was the mucosa penetrated. In the other methods, particularly method 5, the distortion caused by the first anterior catgut suture was, as previously noted, so pronounced that it was technically difficult to place the silk sutures accurately, with resultant penetration of the intestinal mucosa. Particularly is this true when one uses curved needles on a needle holder. Then, we believe, it is virtually impossible, as was first pointed out by Halsted [14] and recently experienced by one of us,[20] to "sense" the depth to which one's needle is penetrating, provided one is attempting to engage the outermost portion of the submucosa.

We are not able to state the ultimate fate of our silk sutures because our specimens, with one exception, were not over twenty-seven days old. Furthermore, our material was not studied primarily for this purpose, which would require some clearing method such as that employed by Reichert and Holman,[21] which would render it unsuitable for histo-

20. Martzloff, K. H., and Burget, G. E.: The Closed Intestinal Loop: III. Aseptic End-to-End Intestinal Anastomosis and a Method for Making a Closed Intestinal Loop Suitable for Physiologic Studies, Arch. Surg. **23**:26 (July) 1931.

21. Reichert, F. L., and Holman, E.: The Fate of Sutures as Observed in Intestinal Anastomosis and in the Healing of Wounds, Bull. Johns Hopkins Hosp. **36**:212, 1925.

logic study. We therefore report our observations for what they may be worth. In a few of our specimens we observed obvious migration of frayed silk particles toward the serosa, but none lying directly beneath it. None of our specimens, even those which had obviously damaged intestinal mucosa and were associated with mucosal suture inclusions, showed silk in the gastro-intestinal lumen. We do not infer from this that luminal migration does not occur, for it obviously does, as we shall be able to report in another paper.

In so far as our observations are concerned, it appears to us that 00 plain catgut is a satisfactory hemostatic suture; it is generally absorbed by the sixth postoperative day; while it does show histologic evidence of damage to the stomach and intestinal walls, where it transfixes them, the mucosal defects (not to be confused with the mucosal defect in the line of apposition) are healed by the sixth day; mucosa apparently does not grow along catgut defects as produced in our experiments; there is considerably more inflammation in suture lines when catgut is employed as we have used it than in methods that avoid its use.

We have made no experiments to see whether 00 plain catgut used as a serosubmucosal suture which penetrates the mucosa will give rise to mucosal suture inclusions.

Silk suture material, when fine and accurately placed, appears to us an ideal suture material in that it evokes practically no inflammatory reaction and permits almost primary healing. However, when silk suture material as used in our experiments is placed sufficiently deeply to penetrate the intestinal mucosa, it becomes involved in varying degrees of inflammatory reaction and in some instances is associated with mucosal inclusions.

The size of the gastro-intestinal ostia, as previously noted, could not be accurately studied in view of the fact that the fresh material was immediately fixed with the minimum of manipulation. The fixed specimens when sectioned, however, showed ostia the greatest dimensions of which varied considerably because of variation in the size of the animals used. None of the ostia was less than 2.5 cm. in length. The amount of inturned stomach and intestine varied according to the time after operation and the suture method used. The specimens removed six and nine days after operation showed much more of an inturned flange than those removed later. In fact the main difference between the flange of a six day healing and a twenty-seven day healing specimen was not so much the depth of the flange (from serosa to mucosa) as its width, which was greater in the early specimens owing to edema and cellular infiltration, which generally was least pronounced in suture method 4 (presection technic). In any event, the determination of inturned flange is not exact, for the same operator repeating the same operation must vary somewhat the amount of tissue that he turns in.

Gross evidence of hemorrhage from the free inturned portion of the gastro-intestinal wall was not observed in any of our specimens. However, one twenty day specimen (12) from suture method 1 (Connell technic) showed the lines of apposition almost completely separated by hemorrhage in some sections.

Serosal Adhesions.—Serosal adhesions at the site of operation were observed in all our early healing specimens. They varied considerably, and were never the cause of complications; we thought that probably they were most pronounced with suture method 5. However, after going over our material again, we rather doubt the correctness of this conclusion. A review of this particular point in a third series not included in this report shows that after ninety days only a few filmlike avascular adhesions remained in animals on which suture method 5 was employed.

HEALING OF THE POSTERIOR ASPECT OF GASTRO-ENTEROSTOMY WOUNDS

As will be noted in the illustrations, only two types of suture technic were employed on the posterior wall of the gastro-enterostomy ostium: (1) a two layer method (suture method 2), employing a sero-submucosal continuous 0 black silk suture and an inner row continuous lock-stitch suture of 00 plain catgut that passed through all coats of the stomach and intestine; (2) a three layer method (posterior method 6), in which the previously described sutures were all continuous.

We did not study the posterior ostial healing in all our specimens because of the many duplications.

Six to Nine Day Healing.—In four specimens in which the lock-stitch suture was employed, only one specimen (six days) showed the mucosal defect almost completely covered by regenerated epithelium. All four of these specimens showed marked inflammation in the line of apposition, and one showed considerable hemorrhage. One specimen showed a silk suture directly in the line of apposition and the site of abscess formation.

In three specimens in which the three layer method was employed there was excellent fibrosis along the line of apposition with a moderate cellular infiltration. In one (nine day) specimen epithelium covered the site of the mucosal defect, while the other two showed a granulating ulcer at the site of operative injury to the mucosa. In all seven specimens in which silk sutures were visible they appeared to be working their way toward the lumen.

Fourteen Day Healing.—One specimen in which the three layer method was used showed epithelial regeneration with gland formation. The healing along the line of apposition was excellent, showing a compact fibrous stroma with a slight round cell infiltration. Three specimens in which the lock-stitch method was employed showed epithelial covering of the mucosal defect in one, without gland formation, and a persistent mucosal defect in two. There was much more evidence of inflammation in the line of apposition than in the three layer suture specimens of from six to nine day healing. The silk in two specimens was near the mucosal margin of the anastomosis and was the site of cellular infiltration.

Twenty Day Healing.—Three specimens were studied: two in which the lock-stitch technic was used and one in which the three layer method was employed. The two former specimens showed mucosal regeneration with gland formation, while the latter revealed mucosal union with very little gland formation at the site of operative injury. All the specimens showed a compact fibrous union at the line of apposition and virtually total absence of cellular infiltration. The silk threads in these sections were surrounded by fibroblasts and a hyaline appearing halo, while there was a total absence of leukocytes.

None of these posterior specimens showed mucosal inclusions in the line of apposition.

The foregoing descriptions indicate that in the early stages of healing (six to fourteen days) the three layer method presents more compact union and is complicated by much less inflammation and hemorrhage than the lock-stitch suture. Our data suggest, but do not prove conclusively, that mucosal healing also is probably accomplished earlier in the three layer method. At the end of twenty days there is little histologic difference between the two. In any event the three layer method, on the basis of its excellent early healing, is the preferable one of the two.

In order to make this comparative study more complete, we are now reporting our results with two other posterior suture methods from a third series of animals that so far have not been included in this paper. Other investigators [22] generally voice the opinion that suture of the mucosa is necessary for its rapid healing. In view of the surprisingly good healing obtained anteriorly with suture method 4 (presection), in which no sutures are passed through the mucosa, we decided to try two other posterior methods of suture: one, a two layer posterior method in which the inner catgut suture pierced the entire thickness of the gastro-intestinal wall, except the mucosa, but did not cross or suture the free edge of the mucosa, and the other an ordinary continuous through-and-through suture method similar to anterior method 5. The former method we designated posterior suture method 7; the latter, posterior suture method 5. These sutures are described earlier in the paper, although it should be noted that in posterior method 7, a good bite in the submucosa is necessary if one is to secure even a modicum of hemostasis, and in doing this it is probably inevitable that the intestinal mucosa is pierced occasionally. It should also be noted that when the gastric and intestinal mucosae are sectioned in posterior method 7, they evert, touch and cover the line of suture.

In view of the poor immediate healing with the lock-stitch suture, it seemed interesting to know just how well healing occurred when the posterior ostial suture penetrated all thicknesses of the gastro-intestinal wall as an ordinary continuous suture (posterior method 5).

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22. Klose and Rosenbaum-Canné (footnote 9).   Strauch (footnote 13).

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POSTERIOR METHOD 7.—Four animals were subjected to this technic and were killed at six, nine, eleven and fourteen days. The healing was remarkable. Six day healing (dog 64) revealed altered glandular mucosa at the site of operative injury, as shown in figure 18. The muscularis mucosae showed only a very narrow defect, while the line of apposition showed a compact granulation tissue with here and there a few aggregations of polymorphonuclear leukocytes. Nine day healing (dog 70) showed the operative site covered with columnar epithelium, while the line of apposition showed less inflammation than in dog 64. Eleven day healing (dog 65) was merely an improvement of that in the nine day specimen. The gastric and intestinal glands were apposed, and there was a conspicuous absence of a broad plateau between gastric and intestinal mucosae. Parietal cells in the gastric mucosa were present within about four gland-widths of the site of gastro-intestinal union. A silk suture was present and had an enveloping hyaline zone. Fourteen day healing (dog 71) showed virtually no evidence of inflammation from mucosa to peritoneum, while the gastric and intestinal glands were closely apposed. A silk suture was passing into the intestinal lumen to one side of the line of apposition, and had some intestinal epithelium about it.

POSTERIOR METHOD 5.—Posterior suture method 5 was used on one animal (dog 72). Nine day healing showed mucosal healing with beginning invagination of the young epithelium for new crypt formation. The line of apposition showed compact granulation tissue with little cellular infiltration. The gastric mucosa at a short distance from the line of apposition showed a rather characteristic change at a point where the stomach wall was pierced by the catgut suture. Here the gastric mucosa had lost its characteristic appearance. The epithelial nuclei and cytoplasm assumed a deeper stain; glands were found; one was rather large and resembled somewhat the marginal cyst on the gastric side of the healed mucosal defect in the same section. Marginal cysts were found in all our posterior suture methods.

The foregoing observations indicate, we believe, that posterior suture methods 5 and 7 are decidedly superior to the lock-stitch suture and also surpass the three layer technic in so far as early healing is concerned.

The complicated healing observed with the lock-stitch method is evidently due to its strangulating effect. This is probably a reasonable inference in view of the rapid and excellent nine day healing obtained with posterior technic 5, which, while it penetrates all coats of stomach and intestine as the lock-stitch does, does not similarly constrict the tissues lying on the ostial aspect of the suture. Obviously, one experiment with posterior method 5 is inadequate and does not warrant the drawing of conclusions.

A comparison of posterior methods 7 and 5 and the three layer technic demonstrates fairly conclusively not only that mucosal suture is unnecessary for early and satisfactory healing but that so-called mucosal suture retards mucosal regeneration. Our findings in this respect corroborate those of Kopyloff, and we can see no logical reason for a posterior three layer suture method. There seems to be little choice between posterior methods 5 and 7, from the standpoint of histo-

logic healing, though technically method 5 is the simpler and more effective for hemostasis. The lock-stitch suture appears most undesirable of all, so far as early uncomplicated healing is concerned. However, it must be admitted that so far as remote healing is concerned, all four methods apparently give the same ultimate result.

Continuous Silk Sutures.—Our observations in this study indicate that, as a general rule, there is a tendency for the posterior continuous serosubmucosal silk suture to migrate toward the gastro-intestinal lumen and to be associated with varying degrees of inflammatory reaction. There are exceptions to this, for in some sections no silk was seen, while in others the silk showed neither evidence of surrounding inflammatory reaction nor a tendency to migrate toward the mucosa.

Actual penetration of the intestinal mucosa by a silk suture was observed only once (dog 71) and indicates that even here, where the suture is placed before any distortion makes its accurate placement difficult, the intestinal lumen may be pierced inadvertently and lead to epithelial inclusions in the intestinal wall. No appositional rests were observed in any of the sections from the posterior aspects of the gastro-intestinal ostia, and this would substantiate our observations on anterior ostial healing, that mere penetration of the entire thickness of stomach and intestinal wall by plain 00 catgut is not a factor in the production of mucosal inclusions in the line of apposition.

SUMMARY AND CONCLUSIONS

This study is based altogether on experimental observations on forty-four dogs. Anterior gastroduodenostomies were performed by various suture methods, while the suture material was uniform throughout.

A group of five dogs from another series was utilized in this report to give a more complete comparison of healing on the posterior aspect of the gastroduodenal ostium.

The purpose of this study was to determine whether serosal cysts would form between apposed peritoneal surfaces and also what differences, if any, occurred in healing following the use of various suture methods.

Our most rapid and uncomplicated healing on the anterior aspect of the gastroduodenal ostium was obtained by the use of a single layer of serosubmucosal presection silk sutures (Halsted), which were termed suture method 4. This observation indicates, we believe, that separate suture of the mucosa (mucosa and submucosa), whether employed anteriorly or posteriorly as in the three layer suture methods, not only is unnecessary for rapid mucosal healing, but is probably a retarding factor and therefore an undesirable as well as an added technical step.

It also emphasizes the adequacy and desirability of the single layer suture method of Halsted, when applicable.

Our next most rapid anterior healing occurred with suture methods 1 (Connell), 3 (baseball stitch) and 6 (three tier). From the single standpoint of firm union along the line of apposition they offer not much difference, while suture method 5 (ordinary continuous suture) in some of the early healing preparations showed most profound inflammatory changes.

Mucosal healing, like healing along the line of apposition, was most rapid with method 4 (one layer presection sutures). Next in order of rapidity is method 3, followed by methods 6, 5 and 1, with probably little choice between the latter three on this particular point.

Our observations indicate that mucosal inclusions develop in the intestinal wall when the mucosa is pierced by a silk suture. This observation, originally made by Mall, has been confirmed by Flint. Other observers have noted these inclusions, but apparently do not recognize their etiology or possible significance.

Sutures placed on the anterior aspect of the gastroduodenal ostium so as to evert the mucosa often cause the displaced epithelium to develop in the line of gastroduodenal apposition, as a persistent adenomatous structure of varying size. The two suture methods (technics 3 and 5) generally advised by English surgical textbooks possess this unrecognized, undesirable and easily avoidable technical fault; it is therefore questionable whether the recommendation of some authors to use suture methods that evert gastro-intestinal mucosa for purposes of hemostasis is sound advice.

Four types of suture methods were used on the posterior aspect of the gastroduodenal ostium. Our best healing was obtained either with an inner row suture passed through all coats of stomach and intestine as an ordinary continuous stitch or with a similar suture passed through serosa and submucosa leaving the cut edges of the mucosa free. The latter confirms our observations on the anterior aspect of the ostium, that separate suture of the mucosa is not necessary for rapid mucosal healing. Next best posterior healing was obtained with the three layer suture technic, and most undesirable of all was the healing following the use of an inner row lock-stitch suture, which we believe has a strangulating effect on the involved tissue.

It is therefore evident that there is a distinct difference in healing following gastroduodenal anastomosis depending on the suture method employed. However, in all fairness to the Connell stitch anteriorly and the lock stitch posteriorly, we admit that no untoward complications developed from their use, and firm healing eventually occurred.

We believe that our observations warrant the conclusion that fine plain catgut, when passed through the entire thickness of stomach or

intestinal wall, does not cause the development of mucosal inclusions along the course of the suture, as in the case of improperly placed silk suture material. However, through-and-through catgut sutures as used by us on the anterior aspect of the gastroduodenal ostium produces decidedly more inflammatory reaction in the healing process than methods in which they are not used; this is particularly true of the Connell suture, which probably acts as a strangulating agent.

Our observations also indicate that when silk suture material is placed without piercing the gastro-intestinal lumen, its presence causes practically no inflammatory reaction. Halsted sutures so placed tend to migrate toward the serosa, while those that pierce the mucosa become infected, are the cause of mucosal inclusions in the intestinal wall and slough into the lumen either through the intestinal wall or along the line of apposition.

If silk suture material is used, it is probably preferable to use interrupted sutures. While our observations are not conclusive, they are most suggestive that continuous silk serosubmucosal sutures show a definite tendency to migrate toward the mucosa. The reason for this is probably that if the continuous suture penetrates the mucosa at any one point, the entire suture may serve as a track along which the inevitable infection may spread. We therefore consider the continuous silk suture as undesirable for gastro-intestinal anastomosis.

Nothing that could be interpreted as a serosal inclusion was observed in this study, and the conclusion is probably justified that serosal inclusions, if they do form, are at best rare occurrences in which serosal surfaces unite under an inflammatory stimulus.

No experiments were done in which so-called redundant mucosa was excised prior to suture of the anterior aspect of the gastroduodenal ostium. We believe that our observations suggest the inadvisability of such a procedure, although it is one still commonly practiced, since none of our specimens showed overlapping of gastric and intestinal mucosa at the line of anastomosis. In fact, with some suture methods well marked mucosal defects occur which would probably be considerably enlarged by the excision of additional mucosa.

ETIOLOGY OF GALLSTONES

IV. IS CHOLESTEROL EXCRETED BY THE GALLBLADDER MUCOSA?

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Ever since the early investigations of Naunyn [1] and his associates,[2] the problem of an excretion of cholesterol and calcium by the gallbladder has remained unsettled in spite of considerable literature on the subject. Since many of these studies were made, the ideas of cholesterol metabolism have undergone such radical changes that a restatement of a few basic facts is important.

To begin with, when cholesterol is mentioned, one is apt to think at once of the liver and bile as the important organ in its metabolism. This is totally unwarranted in the light of modern knowledge. In man, the blood contains about twice as much cholesterol as the bile. According to the work of Sperry [3] and others,[4] reviewed in a previous paper, the overwhelming proportion of the cholesterol excreted is excreted in the intestinal mucosa, this being a far more important route than the biliary. In the dog, the commonest experimental animal used in studies of gallstones, the discrepancy is still more marked. The blood of the dog has a much higher cholesterol content than that of man; the

1. Naunyn, B.: A Treatise on Cholelithiasis, London, New Sydenham Society, 1896.

2. Thomas: Ueber Abhängigkeit der Absonderung und Zusammensetzung der Galle von der Nahrung, Diss., Strassburg, 1890. Kansch: Ueber den Gehalt der Leber an Galle und Cholesterin, Diss., Strassburg, 1891. Jankau, L.: Ueber Cholesterin und Kalkausscheidung mit der Galle, Arch. f. exper. Path. u. Pharmakol. **19**:237, 1891.

3. Sperry, W. M.: Lipoid Excretion: IV. A Study of the Relationship of Bile to the Fecal Lipoids with Special Reference to Certain Problems of Sterol Metabolism, J. Biol. Chem. **182**:351, 1926-1927.

4. Buerger, M., and Oeter, H. D.: Ueber den Cholesteringehalt der menschlichen Darmwand, Ztschr. f. physiol. Chem. **182**:141, 1929. Beumer, H., and Hepner, F.: Ueber die Ausscheidungswege des Cholesterins, Ztschr. f. d. ges. exper. Med. **64**:797, 1929.

normal level is from 200 to 300 mg. per hundred cubic centimeters. This is in marked contrast with the exceedingly low figures found for the hepatic bile of the dog, in which from 10 to 20 mg. per hundred cubic centimeters is the average.

Next is the fact, first mentioned by Rous and McMaster,[5] that the biliary tract is exceedingly sensitive to infection if a fistula is established. They were able to keep the bile in their dogs sterile only by inserting a very long tube, which was allowed to coil up in the abdomen before it was led to the surface. If this precaution was neglected, the bile soon became infected and had a heavy sediment. We called attention in a previous paper [6] to the fact that if stasis occurs in the biliary tract of a dog, especially if the cystic duct is ligated, a prompt endogenous infection of the bile occurs. Pus cells and bacteria can be found in abundance in the bile, and microscopic examination reveals infection of the gallbladder, especially on its hepatic surfaces. This work makes it obvious that in most experimental procedures on gallbladders of dogs one has the element of infection to consider.

Naunyn early called attention to the fact that pus contained a high percentage of cholesterol. This content averages about 300 mg. per hundred cubic centimeters, and in many specimens, as high as 500 mg. per hundred cubic centimeters. It is obvious, therefore, that even a minimal infection raises the cholesterol content of the bile of dogs to many times its normal content.

With these points in view, we shall consider but a single one of the recent publications on the subject of secretion of cholesterol into the gallbladder, that of Elman and Graham.[7] These authors found that the gallbladder added cholesterol to the bile in considerable amounts, which they could not account for in any way except as a secretion of its mucosa. The specimens were secured by aspiration of the gallbladder through the liver substance so as to prevent leakage of bile. A short calculation shows that if but a few drops of blood or serum leaked through the needle hole into the gallbladder, these would account for even the highest rise reported, 300 per cent. This does not take into consideration the possibility of increase of the cholesterol content from leukocytes, which disintegrate rather rapidly in bile.

The problem of the solution of cholesterol-containing débris by bile is a difficult one to answer until it is discovered how it is held in

5. Rous, P., and McMaster, P. D.: A Method for the Permanent Sterile Drainage of Intraabdominal Ducts as Applied to the Common Duct, J.Exper.Med. **37:**11, 1923.

6. Andrews, E., and Hrdina, L.: Hepatogenous Cholecystitis, Arch. Surg. **23:**201 (Aug.) 1931.

7. Elman, R., and Graham, E. A.: The Pathogenesis of "Strawberry" Gallbladder, Arch. Surg. **24:**14 (Jan.) 1932.

solution in the blood. Cholesterol is insoluble in blood serum in vitro, and it is probably held in some chemical compound with the proteins. As to the bile, cholesterol is very slightly soluble in solutions of bile salts, not nearly to the amounts of the normal content of human bile. It has been shown by us in a previous paper [8] that it is not simply dissolved, but is held in a definite chemical compound with the various bile acids that have the power to make it soluble in very high concentrations in an additional compound, the isolation and also the synthetic preparation of which was described. In experimental work on dogs it is exceedingly difficult to tell if the cholesterol in infected bile is really in solution or not, as it may be present in such a very fine amorphous state that it passes rapidly through filter paper, leaving cloudy filtrates even after the leukocytes have been removed.

Our own experiences bearing on this subject have been from the analysis of the content of hydropic gallbladders whether with or without calcium carbonate stones. The results have been as follows:

1. In all clinical cases of long-standing obstruction of the cystic duct in which all the bile salts and pigment have been absorbed, there has been absolutely no cholesterol held in solution; it was all in the form of a crystalline emulsion. It seems, therefore, that there is no substance other than bile salts in the bile capable of holding the cholesterol in solution. This speaks against the origin of gallbladder cholesterol from the body fluids, where it is probably held in solution in some other matter. Although obviously some such material must pass into the gallbladder, its solubility in the other substance enables it to be reabsorbed.

2. Although the amount of cholesterol in the contents from hydropic gallbladders is often much higher than is found in normal bile (up to 600 mg. per hundred cubic centimeters), it has never been our experience to find a greater total in the gallbladder than one would theoretically expect to get from the precipitation of the normal amount of cholesterol from the average human gallbladder (volume from 35 to 40 cc.).

If the bile acids have all been absorbed as they usually have in long-standing hydrops, the cholesterol is always in the form of an emulsion and none is in solution. If cholesterol were excreted in the gallbladder, one would naturally expect to find a far larger amount than that theoretically expected to be derived from the bile in the gallbladder at the time the obstruction of the cystic duct took place. Graham's figures on the cholesterol content of the hydropic gallbladder show a cholesterol content actually below that to be expected, and hence in our opinion do not indicate any excretion by the gallbladder mucosa.

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8. Andrews, E.: Schoenheimer, R., and Hrdina, L.: Studies on the Etiology of Gallstones: I. Chemical Factors and the Rôle of the Gallbladder, Arch. Surg. **25**:796 (Oct.) 1932.

3. The cholesterol is almost uniformly crystalline in form, indicating that it has come from the bile and not from the débris of cells, when it would naturally be in the amorphous form. This statement cannot be considered as final, as it is impossible to tell in a smear whether one is seeing cholesterol in amorphous form or the calcium carbonate, which may greatly exceed it in amount. One can positively state, however, that the débris always contains cholesterol crystals.

In a recent communication, Phemister and his co-workers [9] showed that if the human cystic duct is obstructed for long periods, there is an excretion into the gallbladder of large amounts of calcium. This is in the form of a white, creamy emulsion of almost pure calcium carbonate. Furthermore, if cholesterol stones are already present, obstruction of the cystic duct will bring about a deposit of calcium on the periphery of such stones. This study is quite conclusive and is supported by a series of clinical cases and roentgenograms, as well as by stones removed at operation, with analyses of the gallbladder contents. The important point in relation to our studies is that in no case was there present in such gallbladders any increased amount of cholesterol. Of seven gallbladders reported on by Phemister, one contained a trace of cholesterol and the others none.

Experimental studies on this subject, as we have noted in an earlier paragraph, are beset with almost insuperable difficulties. The possible errors from infection in the gallbladder or from the pouring of a little serum or blood are, as we have said, far greater than the expected experimental variations. Light may, however, be thrown on the problem by certain means.

In the first place, experiments with ligature of the common duct are important. If the common duct is ligated, bile will distend the gallbladder, and after it is once filled, will lie there with little further addition from the liver. Its concentration soon reaches a maximum (about 25 per cent total solids), following which there is very slow further absorption of water. Further concentration is a matter of months, not days. Under such conditions, if secretion of cholesterol by the wall of the gallbladder takes place, one would expect that a gradual mounting in the cholesterol content would take place. Added to this is the possibility of infection under these circumstances, which would increase the cholesterol. Graham reported a series of three experiments in which stasic bile showed a marked increase in cholesterol content. This was probably due to leakage of serum or to infection about the needle holes, as we have done a series of forty-two such experi-

9. Phemister, D. B.; Rewbridge, A. G., and Rudisill, H., Jr.: Calcium Carbonate Gall Stones and Calcification of the Gallbladder Following Cystic Duct Obstruction. Ann. Surg. **94**:493, 1931.

ments, omitting the needle puncture and using thirty-seven normal dogs as controls, and as may be seen from the accompanying table, the results are diametrically opposed to Graham's. A study of this long series has not revealed the slightest increase in the bile cholesterol. It varies between 30 and 100 mg. per hundred cubic centimeters, averaging about 50 mg. per hundred cubic centimeters, and in dogs with prolonged obstruction of the common duct it is not only no higher, but on the average slightly lower, being, however, within the limits of experimental error.

Bile from the gallbladders in six human cases of jaundice also were studied, and the figures fell within the normal range of human values.

Attempts were made to study the normal secretion of the isolated gallbladder, most of which were failures. As previously reported by us,[6] if the dog's cystic duct is ligated and the bile washed out and the hole closed, the result will be the prompt onset of a violent sepsis. The viscus will often be filled with a purulent secretion, which of course contains a high sterol content, as does any other pus. Another series

Cholesterol Content of Gallbladder Bile in Stasis

	Av. Content, Mg. per 100 Cc.
Controls: 36 dogs with stasis of 24 hours or less....................	57
42 dogs with ligature of common duct, 3-58 days.................	51

was studied as follows. The gallbladder was isolated by ligature of the cystic duct and brought up to the skin and a drain inserted. The fistula thus produced, for several weeks secreted a purulent material with a high cholesterol content. This secretion gradually became clearer, and the cholesterol content was much less. Finally the drain was removed, and the wound was allowed to heal. After several openings and closings, it finally stayed closed. After several months the animals were put to death; the gallbladders were removed and the contents studied. In several, it was found that the duct had reopened and the gallbladder was full of bile. In several others, the organ was still infected and contained frank pus. Only one experiment had been entirely successful. Dog 268 was operated on on June 3, 1931, drained for about two weeks and was put to death Jan. 12, 1932. In this dog, the findings were remarkably like those reported by Phemister in human beings. The contents of the gallbladder were pure white and consisted of a creamy, viscid, opaque material. The walls were thickened and whitish gray. Microscopic examination showed that no pus cells were present and very few mononuclear cells (about one or two per field). Chemical analysis showed that the gallbladder contents contained but 21 mg. of cholesterol per hundred cubic centimeters and 580 mg. of

calcium per hundred cubic centimeters. This was the only case in our entire series in which it had been possible to get a clean, pus-free secretion from the gallbladder of the dog, and while it is rash to generalize from the result of a single experiment, we believe that it offers some further proof that the excretion of the mucosa of the normal gallbladder is rich in calcium and poor in cholesterol.

Another almost exactly similar observation was made in a clinical case, no. 41658. A woman, 76 years old, had undergone a cholecystostomy twenty-two years before; no bile had drained, but only mucus for several weeks, following which the wound closed and remained so until just before admission when a fistula of the gallbladder was presented. This drained no bile, and the patient was perfectly normal except for the discharge. This was of a double character, being composed mostly of a clear, watery fluid evidently from the gallbladder itself, but also containing an occasional gush of pus from the granulating tract. This interpretation was confirmed at operation in which the tract was excised and a cholecystectomy was done. Chemical studies of the discharge from this fistula showed that the purulent portion of it contained a high percentage of cholesterol, 510 mg. per hundred cubic centimeters. The clear part, however, contained only the faintest trace of cholesterol (less than 1 mg. per hundred cubic centimeters). This offers another confirmation of the fact that the clean secretion of the gallbladder does not take part in the formation of cholesterol stones.

COMMENT

In a previous paper [10] it was shown that infection of a dog's gallbladder caused a marked fall in the calcium content of the stagnant bile.

In the control series, in which it appears that slight infection must have taken place, the fall in the calcium was much less, about 20 per cent as against about 60 per cent in the violently infected ones. These findings are in marked contrast to the secretion of calcium found in the human cases by Phemister and the single successful experiment on a dog reported in a previous paragraph. The explanation probably lies in the reaction of the bile, or more strictly, of the contents of the gallbladder, which in the latter group are generally free from bile salts and pigment. In our earlier experiments there must almost certainly have been a marked fall in the p_H value and acidification of the bile. Rous showed that the bile of the gallbladder underwent marked acidification in the process of concentration in dogs. This, of course, would increase the solubility of the calcium and favor absorption. The exact opposite was shown to be the case by Phemister,[9] who found quite high p_H values in his cases of calcium carbonate milk in the gallbladder. In

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10. Andrews, E., and Hrdina, L.: Absorption of Calcium from the Gall Bladder, Am. J. M. Sc. **181**:478, 1931.

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our single successful experiment on a dog there was not sufficient material to make this determination. However, alkalinity tends to reduce the solubility of calcium and would not favor its absorption.

The problem, then, appears to be answered as follows: In the normal concentrating action of the gallbladder, the calcium is concentrated to about the same extent as the other ingredients of the bile. This was shown by us quite clearly in a former paper.[5] During this process, as Drury[11] and his co-workers showed, marked acidification takes place. This acidification is accentuated by the presence of infection, which is likely to occur in any static bile, and by this means the absorption of calcium is hastened. If however, the cystic duct is closed over very long periods, the bile is absorbed and the tendency to infection overcome. Then the tissue fluids secreted into the gallbladder are unusually alkaline, and calcium is precipitated and accumulated in the form of pure calcium carbonate, the more soluble salts being resorbed.

In the case of cholesterol, the exact opposite is the case. The infection accompanying stasis brings about the excretion of migrating cells containing large amounts of cholesterol as well as serum, which in most animals is richer in cholesterol than even the concentrated bile of the gallbladder. This cholesterol is not in soluble form and cannot be laid down in the crystalline gallstones. This phase of the problem has often been lightly dismissed, but it is impossible to explain chemically the changing of an amorphus débris into a crystalline gallstone. The existence of large crystals implies that cholesterol crystallized out of solution.

If the ducts are open, the slight amount of mucosal secretion will be washed out. If they remain closed, either an abscess develops or sterilization occurs, after which the findings of very low cholesterol values is the usual one. In any event the cholesterol excreted by the mucosa takes no part in the formation of gallstones.

CONCLUSIONS

1. Cholesterol, although excreted by the infected gallbladder, is not excreted in appreciable amounts by the mucosa of the normal gallbladder.

2. The mucosa of the gallbladder takes no part in the formation of cholesterol stones.

3. Calcium is excreted in large amounts by the mucosa of the normal gallbladder, and this is an important factor in the building of gallstones.

11. Drury, D. R.; McMaster, P. D., and Rous, P.: Observations on Some Causes of Gall Stone Formation: III. The Relation of the Reaction of the Bile to Experimental Cholelithiasis, J. Exper. Med. **39**:403, 1924.

CALCINOSIS UNIVERSALIS

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The purpose of this paper is to present a case of a rare condition and a treatment which yielded satisfactory results. The case was observed at frequent intervals for a period of four years.

Since there is considerable similarity between calcinosis universalis and progressive myositis ossificans, there was difficulty in identifying the condition presented by my patient. Because of the presence of true subcutaneous calcareous deposits along the fascial planes and a lack of ossification and involvement of the muscles, the case was considered one of calcinosis universalis.

Calcium deposits have been found previously in many organs and tissues in various conditions, the calcification quite frequently being an end-result of a degenerative process. Generalized calcium deposition of an unknown cause was first described by Verse.[1] Since then other cases have been added to the literature. Not infrequently, associated with calcinosis universalis were other conditions, such as scleroderma, dermatomyositis and myositis fibrosa. Langmead[2] expressed the belief that the cause underlying these four disorders is probably the same.

Various theories were advanced as the cause of calcinosis universalis. Craig and Lyall[3] expressed the belief that it is a disturbance of the calcium-phosphorus balance. A parathyroid dysfunction was advanced as the cause, and parathyroid extract was suggested for treatment. In a child of $3\frac{1}{2}$ years Morse[4] found that the calcification was preceded by a degeneration of fat. Virchow described a condition which he labeled metastatic calcification. Wells,[5] Schulze[6] and others showed that the condition studied by Virchow presents an oversaturation of the blood with calcium salts, and the calcium deposition occurs without a previous

1. Verse, M.: Ueber Calcinosis universalis, Beitr. z. path. Anat. u. z. allg. Path. 53:212, 1912.

2. Langmead, F. S.: Relationship Between Certain Rare Diseases: Scleroderma, Calcinosis, Dermatomyositis, Myositis Fibrosa, Arch. Pediat. 40:112, 1923.

3. Craig, John, and Lyall, Alexander: A Case of Calcinosis Universalis, and a Suggested Method of Treatment, Brit. J. Child. Dis. 28:29, 1931.

4. Morse, John Lovett: Calcification of the Skin in a Child, Am. J. Dis. Child. 22:412 (Oct.) 1921.

5. Wells, H. G.: Metastatic Calcification, Arch. Int. Med. 15:574 (April) 1915; Tr. Chicago Path. Soc. 9:208, 1914-1915.

6. Schulze, F.: Skelettveränderungen als Ursache von Verkalkungen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 36:243, 1923.

degeneration of tissue.   Wells also pointed out that the calcium is deposited in areas in which carbon dioxide is least abundant.

Tisdall and Erb [7] reported two cases of calcium deposition in the skin with normal blood calcium and phosphorus.   They expressed the belief that some local condition was the determining factor in the deposition of calcium.   Bauer, Marble and Bennett,[8] studying the case of Wilens and Derby,[9] did not find fatty degeneration, inflammation or tissue necrosis.   The blood calcium of the patient was normal, and they believed that the calcium deposition was due to an abnormal calcium and phosphorus metabolism.

It is generally agreed that the treatment of calcinosis universalis is futile and the condition is progressive.   Craig and Lyall [3] reported a case in which the calcium disappeared in sixty days following the administration of disodium phosphate.   Kennedy [10] advised a ketogenic diet.   Frolich [11] treated a patient with progressive myositis ossificans with a high fat diet.   He believed that calcium deposition could be prevented by such a diet, basing his view on the gradual disappearance of some of the calcium and an absence of new deposits in his patient.

REPORT OF A CASE

History.—A girl, aged 6½ years, was first seen on Feb. 4, 1928.   She had difficulty in walking because of contraction of both Achilles tendons and a resulting equinus.   She walked on the forepart of her feet.   She had painful and indurated areas on her extremities.   She had had measles at 3 years, "intestinal flu" at 4, whooping cough at 5, tonsillectomy at 5, chickenpox at 6 years and pneumonia three times between the ages of 3 and 5.   Her present difficulty began four years prior to examination when she began to fall down.   Two and a half years later her joints became "stiff."

Examination.—At the time of the first examination she had a temperature of 100 F. and a pulse rate of 90.   The conjunctivae were slightly injected, and the veins of the eyelids were dilated.   There was induration of both pectoralis major muscles as they bridged the axillary space.   The inguinal glands were enlarged. There were also indurated masses in both biceps tendons, and the elbows could not be extended beyond 80 degrees.   The shoulder joints were normal.   The forearms, the hands and the fingers were normal.   There were similar indurated masses in both hips, but with no limitation of motion.   The thighs were indurated, the con-

7. Tisdall, F. F., and Erb, I. H.:   Report of Two Cases with Unusual Calcareous Deposits, Am. J. Dis. Child. **27**:28 (Jan.) 1924.

8. Bauer, W.; Marble, A., and Bennett, G. A.:   Further Studies in a Case of Calcification of Subcutaneous Tissue ("Calcinosis Universalis") in a Child, Am. J. M. Sc. **182**:237, 1931.

9. Wilens, Gustav, and Derby, Joseph: Calcification of Subcutaneous Tissue in a Child (Calcinosis Universalis), Am. J. Dis. Child. **31**:34 (Jan.) 1926.

10. Kennedy, R. L. J.:   Calcinosis and Scleroderma in a Child Treated by Ketogenic Diet, M. Clin. North America **12**:1655, 1929.

11. Frolich, Theodor: La myosite, ossificante progressive, traitée par le jeune hydrocarbone (l'acidose artificielle), Acta pædiat. **5**:294, 1926.

Fig. 1.—Photographs taken after four years of observation. Note the scars on the right thigh and on the right and left buttocks, where calcareous areas broke down; also note the position of the feet.
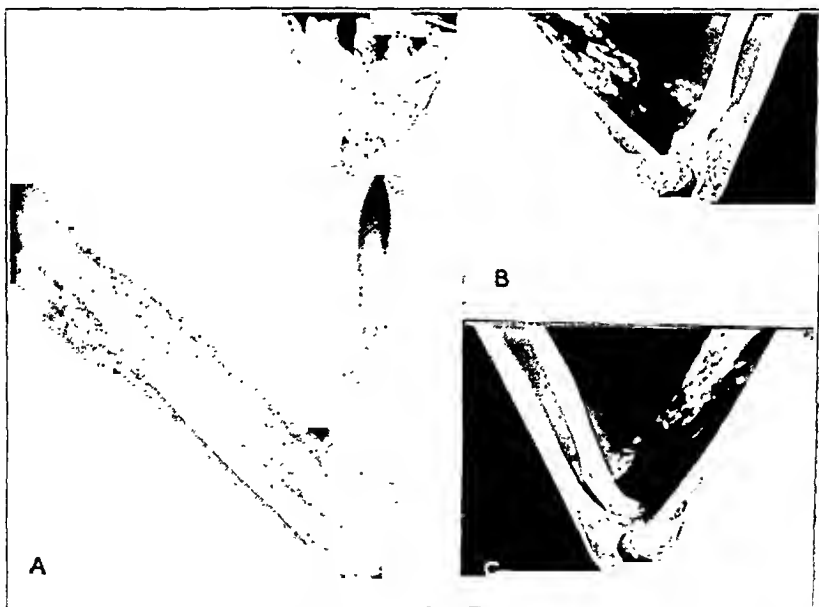
Fig. 2.—Roentgenograms taken at the first examination, in February, 1928. Note the involvement of the biceps muscle in *A,* and also the manner in which the biceps tendons are involved in both elbows (*B* and *C*).
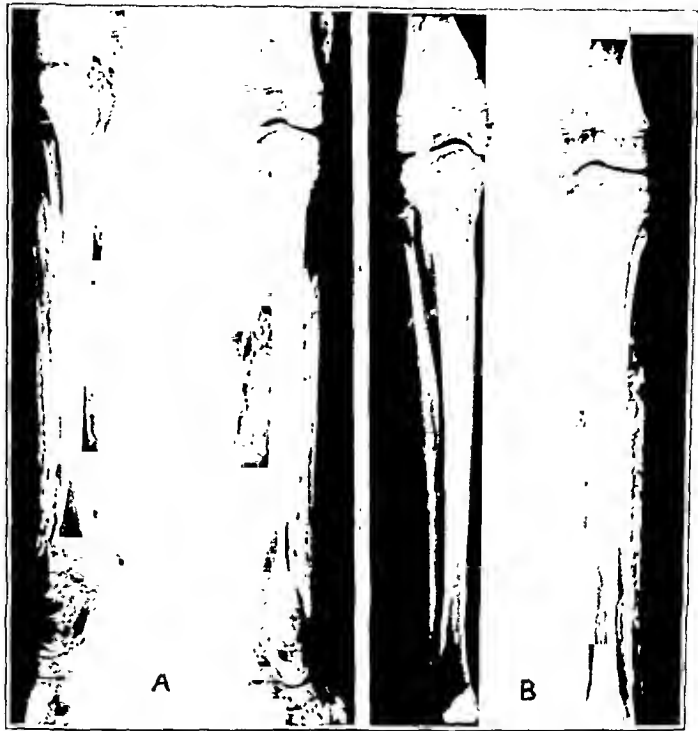
Fig. 3.—*A*, roentgenogram taken in February, 1928. Note the involvement of the extensor tendons to the dorsum of the foot. *B*, roentgenogram taken in October, 1931. Note the marked disappearance of the calcium deposit as contrasted with *A*, taken three years previously.
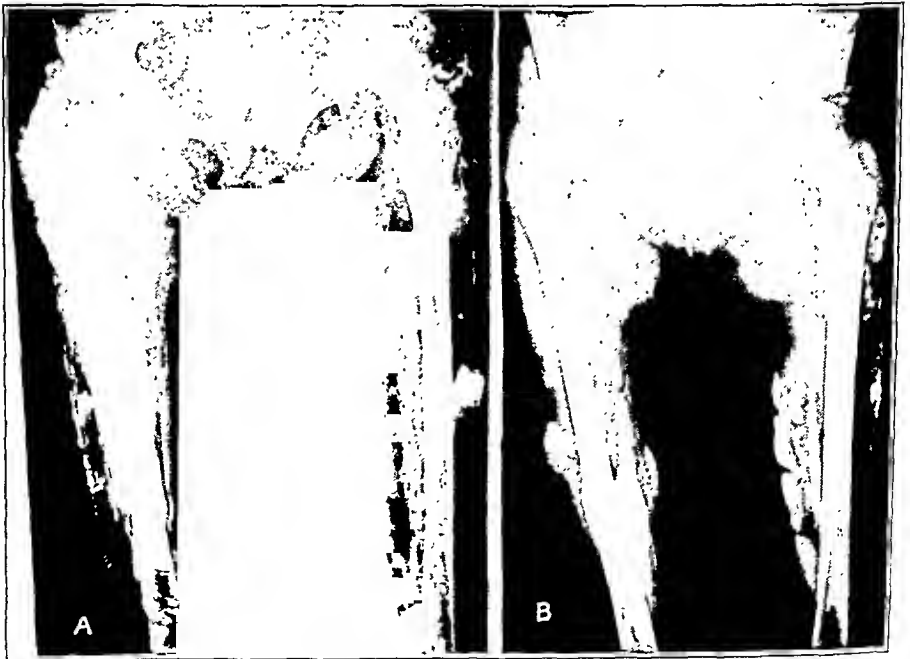
Fig. 4.—*A*, roentgenogram taken in February, 1928. *B*, roentgenogram taken in October, 1931. Note the diminished amount of calcium about the buttocks and thighs as contrasted with the roentgenogram taken three years previously.

dition being more pronounced on the left side. There was contraction of both Achilles tendons with induration of the left one. The right ankle joint was fixed, but there was some motion in the forepart of the right foot. The left ankle joint had a marked limitation of motion. The indurated areas began as small, red, painful, subcutaneous nodules, enlarging progressively and diffusing into the surrounding tissue. The older areas were painless. Often two or more of these nodules coalesced; some of them had a soft center, broke through the skin and discharged calcareous material.

At the first examination, roentgenograms were taken of the entire osseous system. There were marked calcareous deposits along the fascial planes in both
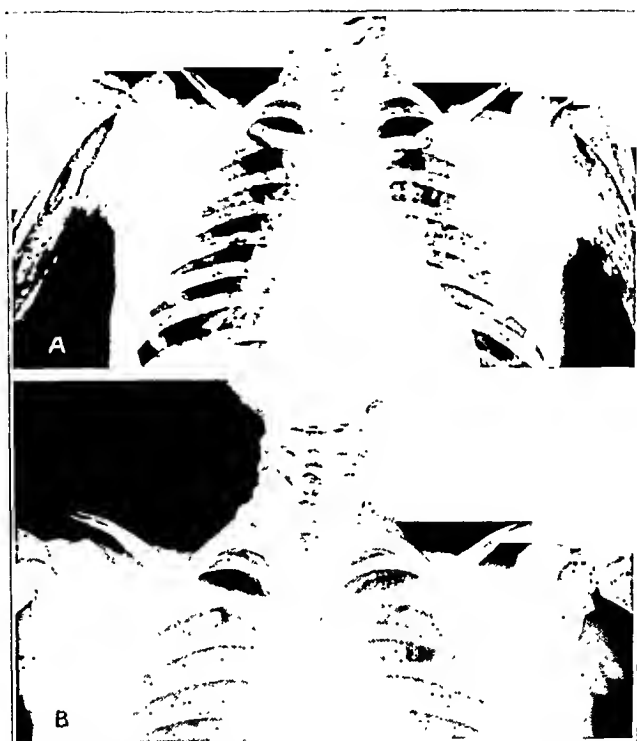
Fig. 5.—*A*, roentgenogram taken in February, 1928. Note the calcareous deposits about the axillae. *B*, roentgenogram taken in October, 1931. Note the marked disappearance of the calcium deposits.

gluteal regions, the thighs, most marked on the left, about both knee joints, the popliteal space, the calves of both legs and along the extensor tendons of the feet. There were also deposits in the pectoralis major muscles and in the upper and posterior parts of the arms, as well as involvement of the biceps tendons.

The white blood count was 7,600, with 68 per cent polymorphonuclears, 32 per cent lymphocytes and 80 per cent hemoglobin; the red blood count was 4,200,000. The reactions to the Wassermann and Pirquet tests were negative. The blood calcium was 16 mg. on Feb. 11, 1928; 11 mg. on May 26, 1928; 10 mg. on Aug. 20, 1930, and 10.8 mg. on Jan. 19, 1932.

A nodule was removed in February, 1928, from the right thigh. The nodule was intimately attached to the fascia lata. Grossly, the tissue was grayish white with small firm granules. Microscopically, the tissue showed a marked infiltration of calcium arranged in globules of varying sizes. The connective tissue was swollen, edematous and, in places, necrotic. There was an occasional giant cell containing calcium granules.

Fig. 6.—Section of a nodule removed from the external aspect of the right thigh in February, 1928. *A* shows deposition of calcium. *B* shows edema and swelling of the tissue, with necrosis in some areas. The entire right edge contains calcium in rather circumscribed nodules of varying sizes. There is an occasional giant cell. There are no bone cells.

Treatment.—The mother noticed a marked improvement in the patient during the summer months, when the child played in the sunshine, and a progression of the disease during the winter months. Because of this observation a course of heliotherapy was outlined. The exposures were gradually increased to cover the entire body daily. The first exposure was for five minutes, which was gradually increased to three or four hours daily. The mercury quartz light was used during the months of the year in which sunshine was not available. This treatment was
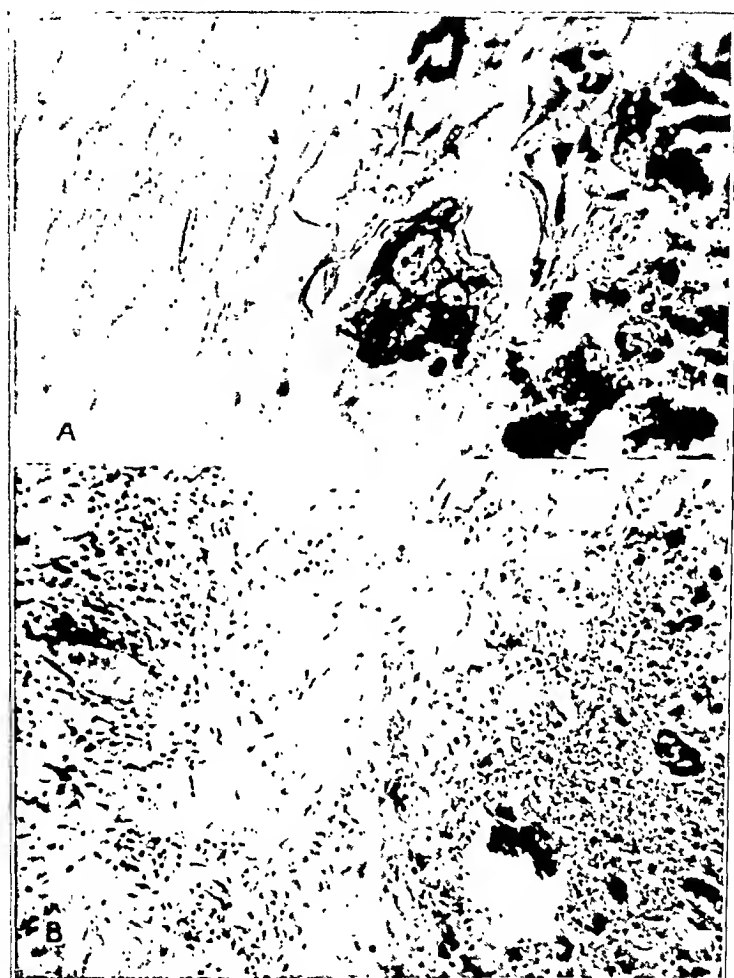
Fig. 7.—Sections removed in October, 1931, three years after the first biopsy. *A* shows numerous giant cells filled with small particles of calcium. The calcium is in small granules instead of large deposits, as seen in figure 6. The connective tissue shows absence of swelling and only slight edema. *B* shows a mononuclear infiltration, giant cells and a granular deposit of calcium.

administered during the four year observation period. No other treatment was given during this time. During the fall, winter and spring of 1929 and 1930, the patient resided in Arizona. After eight weeks of the treatment the blood calcium

fell from 16 to 11 mg. No new painful indurated areas were found. The old areas became painless. The temperature did not rise above 99 F., and the headaches disappeared. Several indurated areas broke down but healed promptly. The roentgenograms taken at six month intervals over four years showed a gradual disappearance of the calcium. A biopsy done in October, 1931, showed numerous giant cells filled with granules of calcium. The calcium deposits consisted of minute granules instead of large masses as in the previous biopsy material. The connective tissue did not show necrosis and swelling and only a slight edema. There was a moderate mononuclear infiltration. It was apparent that the method of removal of calcium was by means of a foreign body giant cell reaction with some unknown factor producing granularity of the large masses of calcium.

SUMMARY

A case of a diffuse calcium deposition in fascias (calcinosis universalis) is presented. Heliotherapy apparently produced a gradual disappearance of the calcium as observed by progressive roentgenograms. There was associated a definite clinical improvement. The removal of the calcium apparently was accomplished by a giant cell reaction preceded by a fine granularity of the large masses of calcium.

Dr. Bernhard Steinberg, Director of Laboratories and Research of Toledo Hospital, assisted me in the pathologic descriptions and the photographs.

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TRAUMATIC ENCEPHALITIS

CASE REPORTS OF SO-CALLED CEREBRAL CONCUSSION WITH ENCEPHALOGRAPHIC FINDINGS

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AND

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OMAHA

The increasing number of cases of trauma of the head presents a problem of major importance to all branches of the medical profession. From automobile accidents alone there were 31,000 deaths in 1931 in the United States, and the total number of accidents for the year extended into the millions. Injuries of the head are frequent among such accidents.

There has been a marked therapeutic advance in the management of the severer types of acute injuries of the head in the past decade, owing to the increasing general knowledge of the diagnosis and treatment of cerebral edema and hemorrhage. Also, the surgical indications are fairly well agreed on by all authorities.

The milder degrees of cerebral trauma, which at the time of the accident are usually called cerebral concussion, representing types of injury to the brain without acutely increased intracranial pressure, with or without fracture of the skull, have not in our opinion received the study they deserve. In the past the results of treatment of this group of patients, in which there is a large number, have been unsatisfactory. A large percentage of the patients have residual complaints, and the question as to whether their complaints were on a psychogenic or an organic basis has not been clear.

Some of the patients show diffuse neurologic signs, mental symptoms, personality changes, palsies of the cranial nerves and bilateral findings, but no focal signs. These findings are not entirely attributable to cerebral edema, but are probably the result of multiple punctate hemorrhages throughout the brain tissue. This condition is a true type of traumatic encephalitis, and in some cases additional subarachnoid hemorrhage is present.

A much larger group of patients, however, who suffered from so-called concussion, never showed any organic signs of neurologic

structural disease. The acute concussion was presumed to be an essentially transient state not producing structural damage to the nervous system. Nevertheless, the patients continued to complain for long periods of numerous symptoms, such as headache, vertigo, tinnitus, disturbance of sleep and inability to concentrate.

Glaser and Shafer,[1] in a study of 255 cases of trauma of the head, found 140 cases, or 54.9 per cent, without fracture of the skull. They found organic neurologic signs in only 18.5 per cent of these cases. Yet 90 per cent of the group of patients had profound subjective complaints. The studies showed that chronic headaches persisted more often in the group without fracture of the skull than in the group with fracture of the skull. Also, the older the patient, the more likely he was to have prolonged complaints. Unfortunately, their studies were not confirmed by encephalographic examinations.

Pommé and Liégeois [2] reported persistent subjective symptoms in 113 soldiers who sustained wounds of the head during the World War. The patients all had either fracture of the skull or cerebral concussion.

Because of the absence of objective findings on neurologic examination, the conditions in the patients studied were usually diagnosed as posttraumatic psychoneuroses. More recent diagnostic studies of these patients by careful observers have usually shown a characteristic and demonstrable cerebral disorder that exists even without definite neurologic findings. Many of the patients showed reactions similar to those seen following acute epidemic encephalitis.

By the method of encephalography we are able to visualize accurately and to determine the amount of structural damage to the intracranial contents. The more common findings shown by encephalographic studies are extensive cortical or cerebral atrophy, hydrocephalus (external and internal) and arachnoiditis, with obstruction to various cerebrospinal fluid pathways.

The general medical profession is still slow to recognize the tremendous advance in intracranial diagnoses brought about as a result of cerebral visualization by this method. This procedure should be in more general use, as it removes much of the guesswork in clinical neurology. The procedure should be recommended in all cases of cerebral injury in which there is a question of diagnosis. It is of extreme value in certain medicolegal cases in which the question of the

1. Glaser, M. A., and Shafer, F. P.: Skull and Brain Traumas: Their Sequelae: A Clinical Review of Two Hundred and Fifty-Five Cases, J. A. M. A. **98**:271 (Jan. 23) 1932.

2. Pommé, B., and Liégeois, R.: On the Subjective Syndrome Common to Head Injury. Rev. neurol. **1**:483 (April) 1931; quoted in Neurology, Practical Medicine Series, Chicago, Year Book Publishers, Inc., 1931, p. 60.

extent of cerebral damage is present. It gives accurate diagnostic information not obtainable in any other way. It should also be recommended from a therapeutic standpoint. Frazier, Penfield, Fay and others who have made large numbers of encephalograms reported that a percentage of their patients are relieved of severe posttraumatic symptoms.

The pathologic causes of the profound changes seen on encephalography, particularly in cortical atrophy, are in dispute. There are probably several factors, one or more being operative in each case. Fay [3] expressed the belief that traumatic cerebral atrophy is a pressure atrophy due to a disturbance in the cerebrospinal fluid-eliminating mechanism (subarachnoid villi and pacchionian bodies), permitting an increase in the amount of supracortical fluid with pressure. As a result of Bagley's [4] observation of arachnoiditis produced from blood introduced into the subarachnoid spaces, Fay expressed the belief that cerebral trauma producing subarachnoid hemorrhage injures the pacchionian bodies, producing obstruction to the outflow of cerebrospinal fluid, with secondary pressure atrophy of the cortex.

When necropsy studies have been possible in cases of death resulting from some cause other than concussion, acute cerebral injury in the form of multiple punctate intracerebral hemorrhages has been shown. Osnato and Giliberti,[5] from a review of the literature and their own pathologic studies, found diffuse perivascular hemorrhagic infiltration similar to the perivascular pathology of acute encephalitis. They concluded that cases of concussion do show evidence of structural cerebral injury, and that there is a strong likelihood for secondary degenerative changes to develop. They believe, therefore, that postconcussion neuroses should properly be called traumatic encephalitis.

In mild cases of cerebral trauma that have been carefully observed from the onset, in which intracranial compression symptoms were mild and no pronounced cerebral edema was demonstrable on lumbar puncture and manometric reading and in which the spinal fluid was clear, marked pathologic changes have nevertheless been shown on later encephalography. The concept of traumatic encephalitis explains the pathologic findings better than Fay's concept of pressure atrophy from obstruction. As stated before, however, the combination of factors (cerebral edema, subarachnoid hemorrhage and intracerebral diffuse minute hemorrhages)

3. Fay, Temple: Generalized Pressure Atrophy of the Brain, Tr. Sect. Surg., Gen. & Abd., A. M. A., 1929, p. 186.

4. Bagley, Charles, Jr.: Blood in the Cerebrospinal Fluid: Resultant Functional and Organic Alterations in the Central Nervous System; A. Experimental Data, Arch. Surg. **17**:18 (July) 1928.

5. Osnato, M., and Giliberti, V.: Postconcussion Neurosis—Traumatic Encephalitis: A Conception of Postconcussion Phenomena, Arch. Neurol. & Psychiat. **18**:181 (Aug.) 1927.

probably produces the majority of cases of cortical atrophy. Obliterative arachnoiditis is best explained by previous subarachnoidal hemorrhage.

Variations in the size, contour and position of the ventricles result from a combination of atrophy of the brain and subarachnoidal changes which may produce traction through adhesions or pulsion through a cystic expansion of the supracortical channels. Atrophy of the parenchyma of the brain without peripheral fixation of the cortex by subarachnoidal adhesions or without a block between the ventricles and subarachnoidal spaces may lead to extensive widening of the arachnoidal channels and yet may cause little change in the ventricles. Asymmetric atrophy of the brain may lead to an unbalanced enlargement or distortion of the ventricles or subarachnoidal channels. Unilateral
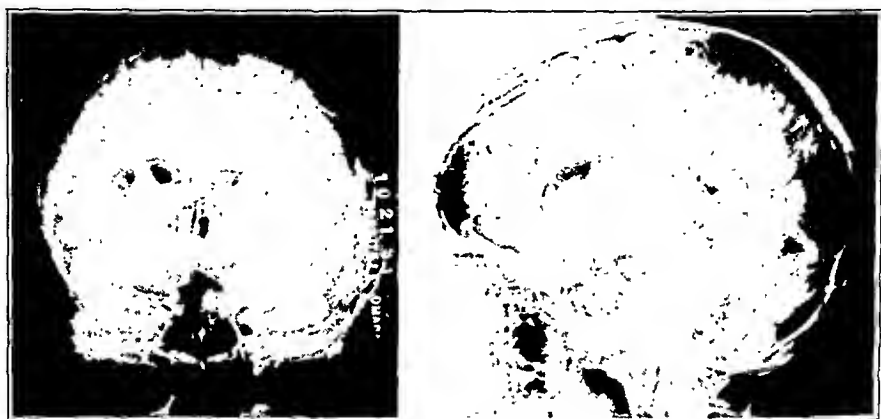
Fig. 1.—An essentially normal encephalographic study which shows clearly visualized subarachnoidal spaces distributed symmetrically over the cerebral cortex, about the cerebellum and through the basilar and cisternal channels without evident obliteration, enlargement or distortion. The ventricles are within the limits of normal size, position and contour.

adhesive arachnoiditis will tend to pull the ventricular system toward that side, while cystic expansion within the subarachnoidal or subdural region will tend to push the ventricles toward the opposite side. Symmetrical obliteration of the subarachnoidal spaces and absorption pathways, unattended by localized atrophy of the brain secondary to punctate hemorrhages, will lead to symmetrical atrophy of the brain with consequent symmetrical dilatation of the ventricles.

The following cases illustrate various pathologic findings on encephalography in cerebral trauma without fracture of the skull. These are the so-called cases of cerebral concussion or traumatic encephalitis. The cases also illustrate the marked benefit often obtained in the symptoms of the patient following spinal drainage with air replacement.

REPORT OF CASES [6]

CASE 1.—The birth of F. E., aged 17, had been a difficult breech delivery. The right arm had always been weak and underdeveloped. At 8 years of age he had received a severe kick in the head by a horse. Following this the patient was unconscious for about two hours and had fever for two days. Three weeks later Jacksonian convulsions began over the right half of the body, which became progressively worse. Neurologic examination was negative except for right homonomous hemianopia and spastic paresis of the right arm.

The clinical diagnosis was residual cortical defect from birth hemorrhage of the left rolandic area; secondary traumatic encephalitis.

Encephalography showed (fig. 2) atrophy of the left parietal and occipital lobes.

CASE 2.—Mr. G. W., aged 60, following an automobile accident in 1928, was semiconscious for one week. Progressive memory and a personality defect fol-

Fig. 2 (case 1).—Diffuse atrophy through the parenchyma of the brain, most extensive in the left parietal and occipital lobes of the cerebrum, thereby leading to an extensive local enlargement of the surrounding subarachnoidal space and an expansion of the posterior half of the left lateral ventricle. The right lateral ventricle and subarachnoidal channels are within normal limits. There is gross widening of the subtentorial space and cisterna magna suggestive of cerebellar atrophy.

lowed the injury. Examination in March 1930, revealed no focal signs of neurologic disease; a marked organic psychotic reaction type of psychosis was present.

The clinical diagnosis was cerebral arteriosclerosis with traumatic encephalitis.

Encephalography showed (fig. 3) obliterative arachnoiditis obstructing the basilar subarachnoid channels, with cortical atrophy.

CASE 3.—Mr. C. O., aged 22, had been in an automobile accident in January, 1931. This was followed by a period of unconsciousness in the hospital for seventeen days, but there was no fracture of the skull. He was mentally confused and amnesic for one month. When examined in April, 1931, the complaints were
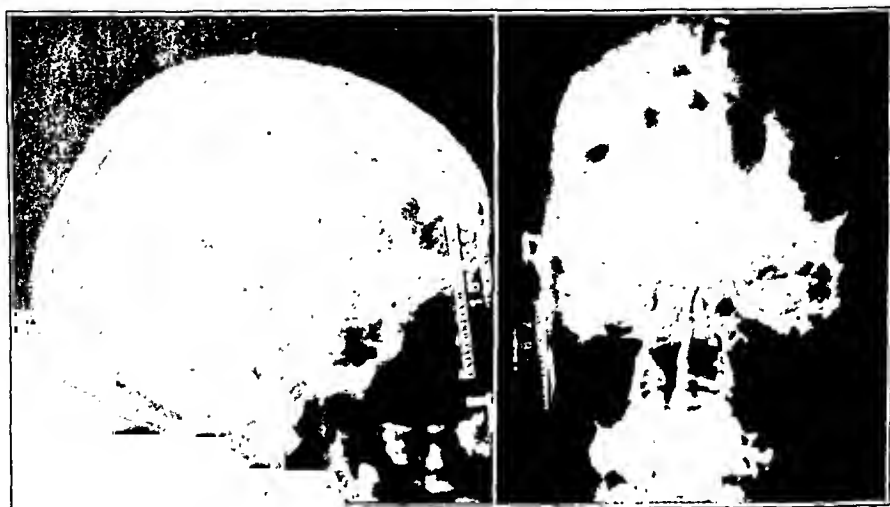
Fig. 3 (case 2).—Relatively complete obliteration of the supracortical sub-arachnoidal channels obstructing absorption of the cerebrospinal fluid and thereby leading to extensive widening of the more proximal subarachnoidal channels along the basilar and temporal regions together with a dilatation of the lateral ventricles and consequent parenchymal atrophy somewhat more extensive in the left side.
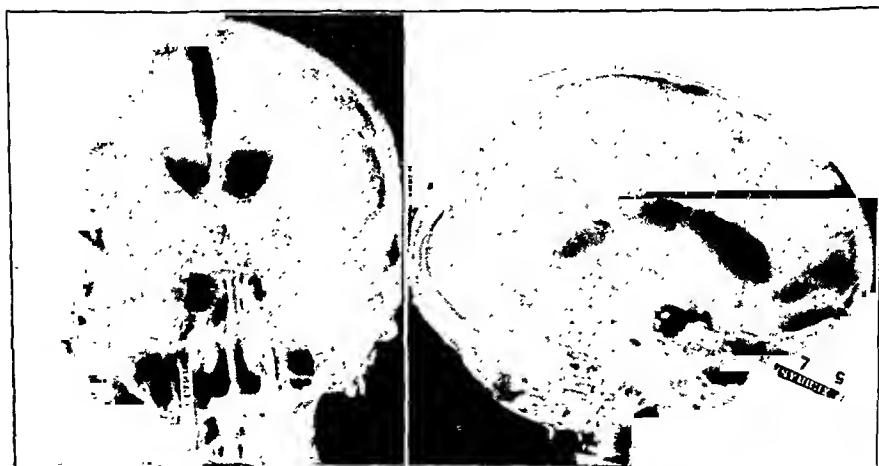
Fig. 4 (case 3).—Relative obliteration of the supracortical subarachnoidal channels, somewhat more complete over the left side of the cerebrum, leading to a moderate distention of the space along the falx and through the basilar cisterns together with dilatation of the lateral ventricles to four or five times the normal capacity and associated parenchymal atrophy, most extensive in the left side.

diplopia and headache. A partial palsy of the right third nerve was the only objective finding.

The clinical diagnosis was traumatic encephalitis and arachnoiditis.

Encephalography showed (fig. 4) bilateral obliterative arachnoiditis with cortical atrophy.

CASE 4.—Mr. H. C., aged 26, in June, 1931, suffered a compound fracture of the nasal bones from a heavy iron crank. The patient was unconscious for a few minutes, and remained in the hospital only three days. Following this he had continual frontal pain, which caused complete disability. Neurologic examination revealed no objective signs of organic disease, and traumatic hysteria was considered.

The clinical diagnosis was indeterminate. Encephalography was done for diagnosis.

Encephalography showed (fig. 5) obliterative arachnoiditis in the frontal areas with cortical atrophy.

Fig. 5 (case 4).—Relative obliteration of the subarachnoidal spaces, most definitely pronounced over the frontal lobes and on the right side associated with slight cerebral atrophy and dilatation of the lateral ventricles, somewhat more extensive in the right frontal area, the lateral ventricle being four or five times the normal capacity.

Only a partial drainage was accomplished, which resulted in a transient improvement of symptoms. Three months later the patient had a second encephalographic study with complete drainage followed by complete relief from symptoms. The same obliterative arachnoiditis was present.

CASE 5.—Mr. L. E., aged 36, in April, 1931, was struck on the right parietal region with a rock weighing 4 pounds (1.8 Kg.) which fell 10 feet (300 cm.). Unconsciousness lasted about ten minutes. The accident was followed by pains in the head, vertigo and persistent nervousness, with an inability to lie on the back or the right side of the head. Neurologic examination revealed no organic signs.

The clinical diagnosis was indeterminate. Encephalography was done for diagnosis.

Encephalography showed (fig. 6) bilateral obliterative arachnoiditis and cortical atrophy. Complete relief from the headache and other symptoms followed the injection of air.

CASE 6.—Mr. C. H., aged 40, had been in an automobile accident in August, 1931, in which he fractured his nose and was unconscious for about two hours. One week later he had febrile delirium for four days, and recovered when the right ear drum ruptured. Persistent headache and a purulent discharge from the ear continued. Examination on October 18 revealed purulent mastoiditis, lateral nystag-
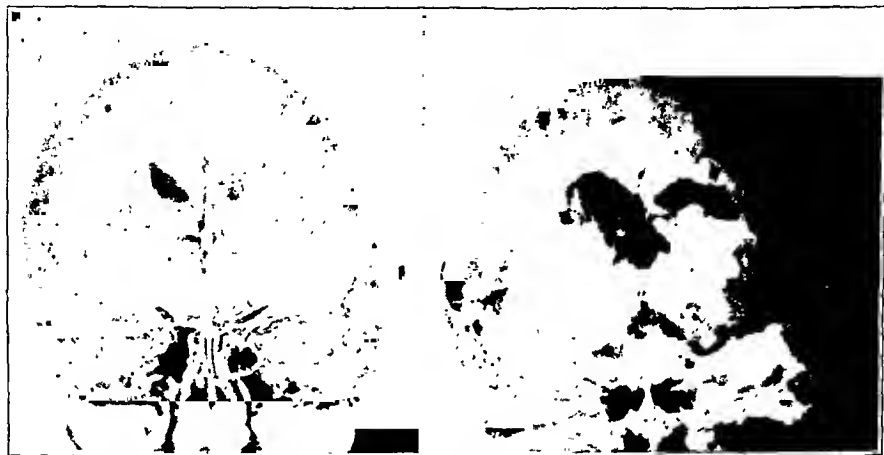
Fig. 6 (case 5).—Slight relative obliteration of the supracortical subarachnoidal channels, most definite over the left side of the cortex, together with enlargement of the left lateral ventricle to three or four times the normal size and with associated slight atrophy through the parenchyma of the left lobe of the cerebrum and slight atrophy through the right lobe.

Fig. 7 (case 6).—Extensive bilateral generalized atrophy of the parenchyma of the cerebrum and cerebellum, leading to an expansion of the subarachnoidal channels over the cortex to a width of 10 or 20 mm. and a gross widening of the cisterna magna and subtentorial space. The ventricles appear normal in size and position, owing to the absence of peripheral fixation of the atrophic brain by adhesive obliterating arachnoiditis.

mus and an increased spinal fluid pressure. A simple mastoidectomy was performed without relieving the headache. A radical mastoidectomy was then performed on

account of the persistent drainage. Encephalography was then carried out on account of the persistent headache.

Encephalography showed (fig. 7) extensive bilateral cortical atrophy. Almost complete relief from symptoms followed the encephalography.

Fig. 8 (case 7).—Marked degree of generalized cortical atrophy leading to a slight widening of the subarachnoidal spaces over the cortex, but without enlargement of the ventricles.

Fig. 9 (case 8).—Extensive obliteration of the subarachnoidal channels about the right side of the cortex, with an associated density confluent with the lateral portion of the right side of the cerebrum. Moderate degree of atrophy through the parenchyma of the left side of the cerebrum, with an associated enlargement of the left ventricle to three or four times the normal size and slight displacement of the ventricles toward the left side.

CASE 7.—Miss A. E., aged 18, four years previously had fallen on cement while roller skating and was unconscious for a few minutes. Severe headache and

vomiting were present for three days. Since that time the patient had suffered from petit mal seizures, vertigo, intense headaches and vomiting. During the past year the patient had been disabled from severe headache and daily vomiting. Examination revealed no objective findings except lateral nystagmoid movements; the cisternal fluid pressure was normal. The spinal fluid pressure with the patient in the upright position, prior to encephalography, was 40 mm. of mercury.

The clinical diagnosis was traumatic encephalitis.

Encephalography showed generalized bilateral cortical atrophy. This patient is still under observation, and is suffering from headache and vomiting; the spinal fluid pressure remains moderately increased. Subtemporal decompression is being considered to give relief.

CASE 8.—Mr. P. R., aged 24, in June, 1931, was thrown against an automobile steering wheel, but was not knocked unconscious. Gradually increasing headache, mental dulness and blurred vision developed. About five weeks after the onset, a subdural hematoma was drained through a right frontotemporal trephine opening. Spinal punctures had shown an elevated pressure. Temporary improvement followed the operation. Because of a recurrence of symptoms, encephalography was carried out on November 9 (fig. 9). On Dec. 3, 1931, Dr. J. J. Keegan performed a right subtemporal decompression, at which time thickened meninges, edematous cortex and flattened convolutions were found.

The clinical diagnosis was traumatic arachnoiditis from a previous subdural hematoma.

Encephalography showed (fig. 9) arachnoiditis and cortical atrophy.

SUMMARY

1. The importance of a more careful diagnostic study of the patient with mild cerebral traumatism is emphasized. In any doubtful case, the study should always include encephalography, which is the only accurate diagnostic method known. Encephalography should be recommended also as a therapeutic agent to relieve posttraumatic symptomatology.

2. The mechanism of production of cortical atrophy is discussed. The cause is usually a combination of factors: (a) an obstructive outflow of cerebrospinal fluid from subarachnoid hemorrhage and edema and (b) diffuse intracerebral punctate hemorrhages or traumatic encephalitis.

3. Eight illustrative case reports with encephalographic findings, showing pronounced cerebral damage from relatively minor injuries of the skull, are included. Therapeutic benefit in the relief of posttraumatic symptoms has been noted in about half of our cases.

EXPERIMENTAL ILEUS

III. PROLONGATION OF LIFE FOR SEVENTY DAYS AFTER HIGH INTESTINAL OBSTRUCTION BY ADMINISTRATION OF SODIUM CHLORIDE AND NUTRITIVE MATERIAL INTO INTESTINE BELOW THE SITE OF OCCLUSION

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Although most investigators and clinicians have attributed death in acute intestinal obstruction to a toxemia, there has been considerable evidence accumulating lately that supports the view that the loss of digestive secretions is an important factor in death from uncomplicated or simple high intestinal obstruction. Gatch, Trusler and Ayres [1] have emphasized the view held by Hausler and Foster [2] that two types of mechanical obstruction must be recognized: (1) acute simple obstruction in which there is simple occlusion of the lumen without circulatory involvement and (2) acute strangulation in which the obstruction is complicated by interference with venous, arterial or lymphatic circulation. As a result of their experiments Gatch and his associates concluded that in the first type, which occurs chiefly high up in the intestinal tract, death was caused by a profound metabolic disturbance resulting from three factors: dehydration, loss of chlorides and starvation. In the second type the same factors were present but were overshadowed by toxemia. They felt that the toxin was not absorbed from the intact mucosa but made its way into the circulation through an overdistended bowel, and in the event of gangrene the absorption by way of the peritoneal surface was rapidly fatal.

In this communication we are concerned with the loss of digestive secretions as an important factor in the explanation of death in uncomplicated high obstruction, and the evidence presented applies to this type

1. Gatch, W. D.; Trusler, H. M., and Ayres, K. D.: Acute Intestinal Obstruction: Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes, Am. J. M. Sc. **173**:649, 1927; Causes of Death in Acute Intestinal Obstruction, Surg., Gynec. & Obst. **46**:332, 1928.

2. Hausler, R. W., and Foster, W. C.: Studies of Acute Intestinal Obstruction: I. Different Types of Obstruction Produced Under Local Anesthesia, Arch. Int. Med. **34**:97 (July) 1924.

of obstruction. The appreciation that the mechanism of death probably is primarily chemical rather than toxic has been made possible by studies of the chemical composition of the blood of obstructed animals and also by experiments with fistulas. The most satisfactory explanation of the chemical nature of death resulting from loss of digestive secretions has been given in a series of articles by Gamble and McIver.[3] They found that the inorganic constituents of the digestive secretions were to a large extent sodium and chloride ion. The continued loss of these secretions depleted the blood plasma and interstitial fluids of the important blood electrolytes, fixed base (chiefly sodium) and chloride ions, without which the body could not hold fluids. Also the relative amounts of sodium and chloride ion lost resulted in an acidosis or an alkalosis of varying degree. They explained the mehanism of death on the basis of dehydration following loss of blood electrolytes, and of distortion of the acid-base equilibrium of the body. They believed that the loss of digestive secretions was an adequate explanation for the cause of death in uncomplicated high obstruction.

The evidence that the loss of digestive secretions is an important factor in the cause of death in high obstruction is offered by experiments involving: (1) administration of sodium chloride solution subcutaneously or intravenously to obstructed animals; (2) short-circuiting digestive secretions below the obstruction; (3) production of fistulas, high intestinal, pancreatic and gastric; (4) administration of substances into the bowel below the obstruction, such as vomitus, sodium chloride, dextrose and peptone.

Hartwell, Hoguet and Beekman[4] were the first to administer sodium chloride solution subcutaneously to animals with intestinal obstruction. By using about 500 cc. daily, they kept three animals with high obstruction alive from twenty-one to twenty-six days, when they were examined and killed. They felt that there were two important factors in death from high obstruction: 1. Loss of water from the tissues caused by excessive drainage into the intestinal lumen followed by vomiting.

3. McIver, M. A., and Gamble, J. L.: Body Fluid Changes Due to Upper Intestinal Obstruction, J. A. M. A. **91**:1589 (Nov. 24) 1928. Gamble, J. L., and McIver, M. A.: The Factor in the Dehydration Following Pyloric Obstruction, J. Clin. Investigation **1**:403, 1925; A Study of the Effect of Pyloric Obstruction, ibid. **1**:531, 1925; The Acid-Base Composition of Gastric Secretions, J. Exper. Med. **48**:837, 1928; The Acid-Base Composition of Pancreatic Juice and Bile, ibid. **48**:849, 1928; Body Fluid Changes Due to Continued Loss of the External Secretion of the Pancreas, ibid. **48**:859, 1928.

4. Hartwell, J. A.; Hoguet, J. P., and Beekman, F.: An Experimental Study of Intestinal Obstruction, Arch. Int. Med. **13**:701 (May) 1914. Hartwell, J. A., and Hoguet, J. P.: Experimental Intestinal Obstruction in Dogs with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, J. A. M. A. **59**:82 (July 13) 1912.

The administration of sodium chloride solution compensated for this loss. 2. The absorption of poisonous material from the intestinal wall when the mucosa was damaged. This factor was not influenced by the saline.

Studies of the chemical composition of the blood of animals with pyloric obstruction were first carried out by MacCallum and his co-workers.[5] They observed a fall in the blood chlorides and an increase in the alkali reserve which they ascribed to loss of gastric juice from vomiting. By treating these animals with sodium chloride solution, the marked changes in the chemical composition of the blood were prevented and life was prolonged. These observations were confirmed by Hastings, Murray and Murray.[6]

Haden and Orr [7] observed a fall in the blood chlorides associated with a rise in the carbon dioxide and nonprotein nitrogen in animals with high intestinal obstruction. This change in the chemical composition of the blood was prevented and life prolonged from three to four weeks by the administration of sodium chloride solution subcutaneously.[8] Death resulted even more rapidly in animals with obstruction that were given injections of distilled water than in those that were untreated.[9] They also found that other salts did not produce the same results as sodium chloride.[10] They concluded that the chloride in the blood was bound by the "toxin" and that the administration of sodium chloride acted as a neutralizer for the "toxin." This view, however, they have since altered and now recognize the "chemical" factors in death from obstruction.[11]

When a considerable part of the digestive secretions are short-circuited below the point of obstruction, animals will live a month.

5. MacCallum, W. G.; Lentz, J.; Vermilye, H. N.; Leggett, T. H., and Boas, E. J.: The Effect of Pyloric Obstruction in Relation to Gastric Tetany, Bull. Johns Hopkins Hosp. **31**:1, 1920.

6. Hastings, A. B.; Murray, C. D., and Murray, H. A.: Certain Chemical Changes in the Blood After Pyloric Obstruction in Dogs, J. Biol. Chem. **46**:223, 1921.

7. Haden, R. L., and Orr, T. G.: Chemical Changes in the Blood of the Dog After Intestinal Obstruction, J. Exper. Med. **37**:365, 1923.

8. Haden, R. L., and Orr, T. G.: The Effect of Sodium Chloride on the Chemical Changes in the Blood of the Dog After Pyloric and Intestinal Obstruction, J. Exper. Med. **38**:55, 1923.

9. Haden, R. L., and Orr, T. G.: Obstruction of the Jejunum: The Effect of Sodium Chloride on the Chemical Changes in the Blood of the Dog, Arch. Surg. **11**:859 (Dec.) 1925.

10. Haden, R. L., and Orr, T. G.: The Effect of Inorganic Salts on the Chemical Changes in the Blood of the Dog After Obstruction of the Duodenum, J. Exper. Med. **39**:321, 1924.

11. Orr, T. G., and Haden. R. L.: Chemical Factors in the Toxemia of Intestinal Obstruction, J. A. M. A. **91**:1529 (Nov. 17) 1928.

One of us (Dr. Jenkins [12]) kept an animal alive thirty-three days by simply short-circuiting the biliary, pancreatic and duodenal secretions beyond the point of a high obstruction. When the same procedure was done on animals with a low obstruction, the average length of life was ten days, although one animal lived twenty days.[13] When animals with a high obstruction on which the same short-circuiting procedure was carried out were given milk and cream along with some sodium chloride through a jejunostomy opening below the obstruction, life was prolonged to thirty-seven days.[14] Pearse [15] kept animals alive a month by short-circuiting the biliary, pancreatic and duodenal secretions and part of the gastric juice below the obstruction, and in addition he introduced milk and cream with some sodium chloride into the distal bowel through a gastrostomy tube in the pyloric part of the stomach. Apparently, there was enough gastric juice resorbed in the obstructed segment or enough diverted below the obstruction, as in Pearse's experiment, to prevent the usual rapidly fatal outcome of complete loss of gastric juice as in Dragstedt's isolated pouches of the entire stomach [16] or from pyloric obstruction.[6] The maintenance of the blood chlorides at a normal level during the period of obstruction when sodium chloride was added to the feedings was apparently due to the replacement of sodium and chloride ions that had been lost in the vomited gastric juice. These short-circuiting experiments are not convincing evidence in themselves that the loss of digestive secretions is an important factor in high obstruction; however, the results may be explained on that basis and warrant mention as such.

In support of the theory there is further evidence in the observations of the changes in the chemical composition of the blood and rapid death of animals that suffer from loss of digestive secretions from high intestinal, pancreatic or gastric fistulas. Walters, Kilgore and Bollman [17] found that in duodenal fistulas the changes in the

12. Jenkins, H. P.: Experimental Ileus: I. High Obstruction with the Biliary, Pancreatic and Duodenal Secretions Short-Circuited Below the Obstructed Point, Arch. Surg. **19**:1072 (Dec.) 1929.

13. Jenkins, H. P., and Roome, N. W.: Low Obstruction with the Biliary, Pancreatic and Duodenal Secretions Short-Circuited Below the Obstructed Point, Proc. Soc. Exper. Biol. & Med. **29**:395 (Jan.) 1932.

14. Jenkins, H. P.: Experimental Ileus: II. High Obstruction with the Biliary, Pancreatic and Duodenal Secretions, Along with Food and Sodium Chloride Entering Bowel Below Obstructed Point, Arch. Surg. **25**:849 (Nov.) 1932.

15. Pearse, H. E.: Is Toxaemia the Cause of Death in Uncomplicated Intestinal Obstruction? Ann. Surg. **93**:915, 1931.

16. Dragstedt, L. R., and Ellis, J. C.: The Fatal Effect of the Total Loss of Gastric Juice, Am. J. Physiol. **93**:407 (June) 1931.

17. Walters, W. Kilgore, A. M., and Bollman, J. L.: Changes in the Blood Resulting from Duodenal Fistula, J. A. M. A. **86**:186 (Jan. 16) 1926.

chemical composition of the blood were an increasing alkalosis, decreasing concentration of chlorides and a progressive rise in blood urea, and that death occurred in from three to four days. Life was prolonged for more than three weeks, and the changes in the chemical composition of the blood were prevented by the daily administration of from 500 to 700 cc. of 1 per cent sodium chloride solution intravenously. The administration of concentrated sodium chloride solution maintained the blood chlorides at a normal level but did not delay death. Dextrose solution (5 per cent) or sodium sulphate did not prolong life or prevent the changes in the chemical composition of the blood. The authors pointed out the similarity between duodenal fistula and high intestinal stasis, and were led to the conclusion that fluid balance played some part in the "toxemia" accompanying duodenal fistula.

Morton and Pearse [18] found that animals with a high obstruction or a high intestinal fistula at the same level died at approximately the same time and showed corresponding changes in the chemical composition of the blood. They felt that death was due to the same mechanism in both instances, i. e., loss of digestive secretions. Elman and Hartmann [19] also found that animals with a high intestinal fistula behaved practically the same as animals with obstruction at the same level (the lower end of the duodenum) as far as changes in the chemical composition of the blood and time of death were concerned. The changes in the chemical composition of the blood were prevented and life was prolonged by the injection of saline solutions in both instances. The mechanism of death was explained on the basis of "chemical changes in the body fluids resulting primarily from loss of gastrointestinal secretions, and secondarily from circulatory and renal insufficiency due to dehydration." They further stated that death in low obstruction was not due to such changes because the chemical composition of the blood was not markedly altered and saline did not appear to influence the length of life; also gangrene or necrosis of the bowel was not necessarily responsible for the lethal outcome.

Elman and McCaughan [20] found that the total loss of the external secretion of the pancreas was fatal in about a week. Elman and Hart-

18. Morton, J. J., and Pearse, H. E.: The Similarity in Effect of Experimental High Intestinal Obstruction and High Complete Intestinal Fistula, Ann. Surg. **94:** 263, 1931.

19. Elman, R., and Hartmann, A. F.: Experimental Obstruction of the Terminal Duodenum and Ileum: Importance of Blood Chemical Changes in Causing Death, Surg., Gynec. & Obst. **53:**307 (Sept.) 1931.

20. Elman, R., and McCaughan, J. M.: On the Collection of the Entire External Secretion of the Pancreas Under Sterile Conditions and the Fatal Effect of the Total Loss of Pancreatic Juice, J. Exper. Med. **45:**561, 1927.

mann[21] studied the chemical composition of the blood of animals with complete pancreatic fistulas and found a fall in chlorides and in the carbon dioxide. In animals that vomited considerably there was an alkalosis instead of an acidosis. These changes in the chemical composition of the blood were prevented by the administration of Ringer's solution, and life was prolonged. They felt that death was due to simple chemical changes brought about by a marked loss of base bicarbonate and a resulting uncompensated acidosis, and that dehydration was also a factor. Dragstedt and his co-workers[22] observed the same changes in the chemical composition of the blood in their experiments on pancreatic fistulas; they prolonged life by the administration of Ringer's solution. Dragstedt and Ellis[16] found that the complete loss of gastric juice from isolated pouches of the stomach was rapidly fatal and was associated with a marked fall in blood chlorides and alkalosis. The chemical composition of the blood remained normal and the life of the animals was prolonged over two months by the daily administration of Ringer's solution. Dragstedt,[23] following the observations on the rapidly fatal effect of the total loss of gastric or pancreatic juice, emphasized that the important factor in death from high intestinal obstruction was the result of failure of reabsorption of gastric and pancreatic juice because of their loss through vomiting.

The most convincing evidence is found in experiments in which material was introduced into the bowel through a jejunostomy opening below the obstruction. White and Fender[24] introduced the animal's vomitus along with water and dextrose into the bowel below the obstruction through a jejunostomy tube. Their animal lived a month. Matsukura[25] injected sodium chloride and water into a jejunostomy opening below the obstruction, and the animal lived thirty-three days. Armour and his co-workers[26] administered sodium chlo-

21. Elman, R., and Hartmann, A. F.: The Cause of Death Following Rapidly the Total Loss of Pancreatic Juice, Arch. Surg. **20**:333 (Feb.) 1930.

22. Dragstedt, L. R.; Montgomery, M. L.; Mathews, W. B., and Ellis, J. C.: Fatal Effect of the Total Loss of Pancreatic Juice, Proc. Soc. Exper. Biol. & Med. **28**:110, 1930.

23. Dragstedt, L. R.: Failure of Reabsorption of Gastric and Pancreatic Juice, Am. J. Surg. **11**:544, 1931.

24. White, J. C., and Fender, F. A.: The Cause in Uncomplicated High Intestinal Obstruction, Arch. Surg. **20**:897 (June) 1930.

25. Matsukura, S.: Chemical Studies on Liver and Other Tissues in Intestinal Obstruction, Closed Loop, Intestinal Fistula, and Perforative Peritonitis, Jap. J. M. Sc. (Tr. Surg. Orthod. & Odont.) **2**:1, 1930.

26. Armour, J. C.; Brown, T. G.; Dunlop, D. M.; Mitchell, T. C.; Searles, H. H., and Stewart, C. P.: Studies on High Intestinal Obstruction: The Administration of Saline and Other Substances by Enterostomy Below Site of Obstruction, Brit. J. Surg. **18**:467, 1931.

ride, dextrose, peptone, water and other substances into a jejunostomy opening below the obstruction. One of their animals lived fifty days. They stressed the point that the withdrawal of sodium chloride from the feedings during the obstructed period would cause death in a few days, with the usual changes in the blood chemistry of untreated obstruction, whereas when the animal was getting sodium chloride, the chemical composition of the blood remained normal. One animal was killed on the forty-fifth day by withdrawing the sodium chloride two days previously, and another had the sodium chloride withdrawn on the forty-fifth day until the changes in the blood chemistry were marked and the animal's condition was obviously critical, when salt was again administered on the forty-seventh day. The condition of the animal improved, and the figures for the chemical composition of the blood returned to normal. This animal had the continuity of the bowel reestablished on the fiftieth day, and from then on improved rapidly. It is probable that the animal would have lived considerably longer than fifty days with the obstruction if the continuity of the bowel had not been reestablished at that time. The work of Armour and his associates was published shortly after the preliminary report [27] of this experiment, in which an animal was kept alive for fifty-two days by the daily administration of about a liter of 1 per cent sodium chloride and 5 per cent dextrose solution into the bowel below the obstruction. Since this report we have kept an animal alive for seventy days by adding peptonized milk to the salt and dextrose feedings.

EXPERIMENTATION

Technic.—The dogs, after being received from the pound, were kept for from two to three weeks in isolation to eliminate distemper. The operations were done under morphine-ether anesthesia. A small left rectus incision was made and the jejunum just beyond the ligament of Treitz delivered. The jejunum was sectioned at varying distances from the ligament of Treitz in the different animals by clamping, ligating, cutting and invaginating the stumps with a linen purse-string suture. The distal stump was always brought to the outside through a stab wound in the right rectus and sutured to the skin (fig. 1). The stump brought to the outside was usually opened at operation after the incision was closed, but in some animals it was not opened until the following day. As soon as the stump was opened, the animal was given from 1,000 to 1,350 cc. of 1 per cent sodium chloride and from 5 to 7 per cent dextrose daily, administered from eight to ten times a day at from an hour and a half to two hour intervals. Occasionally 2 per cent sodium chloride was used for the first few days after operation. When dextrose was given in concentrations greater than 7 per cent, a watery diarrhea usually developed. The weights were taken daily. Determinations of the chemical composition of the blood were made every week or ten days. A control series was obstructed in the same

27. Jenkins, H. P.: Prolonging Life in High Obstruction by Administration of Salt Solution Below Point of Obstruction, Proc. Soc. Exper. Biol. & Med. **28:** 111, 1930.

manner and treated by giving them about a liter of distilled water daily through the jejunostomy opening.

Concerning the chemical composition of the blood, the carbon dioxide capacity or combining power of the plasma was determined in volume per hundred cubic centimeters by the van Slyke method. The total whole blood chlorides were
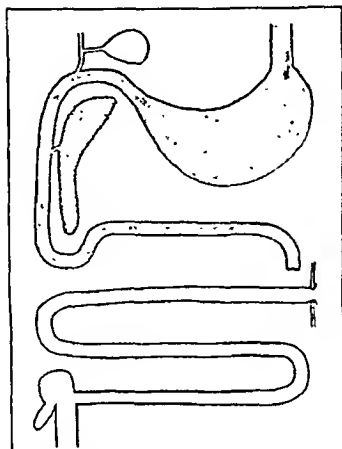
Fig. 1.—Diagram of the operative procedure.
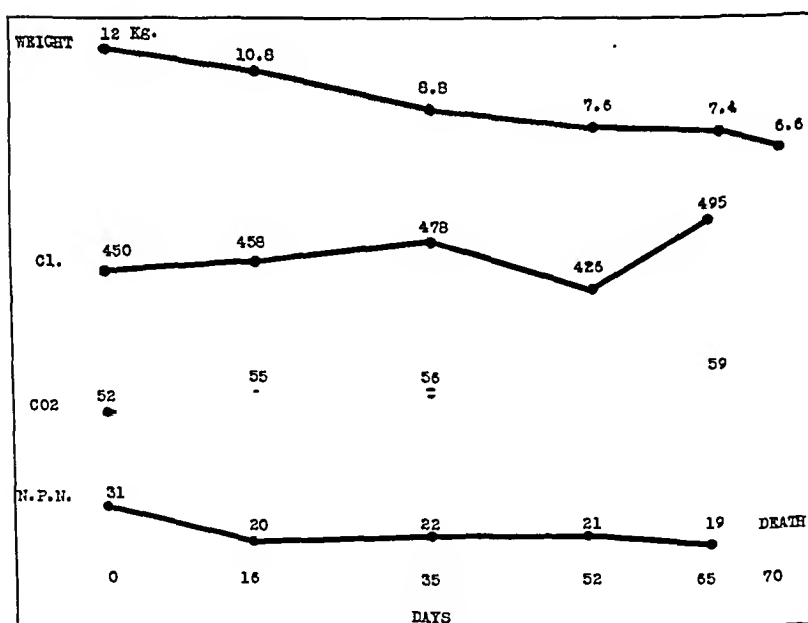
Fig. 2 (dog 660).—Curves of the weight and the figures for the chemical composition of the blood.

estimated as sodium chloride by Whitehorn's modification of Volhard's method. The determinations of nonprotein nitrogen were made by Koch and McMeekin's method.

Protocols.—Series I: Treated with Saline and Nutritive Material Introduced into the Jejunostomy Opening.

Dog 660: The obstruction was made 23 cm. from the pylorus. During the first four days a liter of 1 per cent sodium chloride and 6 per cent dextrose was given through the jejunostomy opening in from eight to nine feedings. From the fifth day on the animal was given approximately 500 cc. of sodium chloride mixture and 500 cc. of peptonized milk. (This was made by adding 1 tube of Fairchild and Foster's peptonizing substance to a pint of milk.) The relative amounts of the salt-dextrose solution and peptonized milk varied occasionally. The animal vomited on thirty-one of the seventy days. The amount of vomitus was not measured because

Fig. 3 (dog 660).—Specimen from the dog, which lived seventy days. The obstructed bowel measured 23 cm.

it was mixed with the urine in the cage. Small formed stools were passed two or three times a week. The weight gradually declined from 12 Kg. before operation to 6.6 Kg. on the seventieth day. This was a loss of 0.0771 Kg., or 0.642 per cent, per day. Studies of the chemical composition of the blood (fig. 2) showed relatively little change during the period of obstruction. The chlorides showed a slight rise from 450 to 495 mg. The nonprotein nitrogen dropped from 31 to 19 mg., and the carbondioxide fluctuated from 52 to 59 mg. The animal showed signs of weakness during the last week which progressed rapidly until the seventieth day, when it was killed while practically moribund. At autopsy a small patch of bronchopneumonia was found. There was no other explanation for the impending death other

than the emaciation from the long-standing obstruction. The 23 cm. of obstructed bowel and the stomach were moderately dilated (fig. 3).

Dog 533: The obstruction was made at a point 95 cm. from the pylorus. It was given 700 cc. of 1 per cent sodium chloride during the first sixteen days. From the seventeenth day on it received 1,000 cc. of 1 per cent sodium chloride and 5 per cent dextrose daily. The feedings were given in 100 cc. amounts at from one and a half to two hour intervals. Vomiting occurred on the average of every other day. Occasionally a slight diarrhea was noticed when the dextrose was poorly tolerated. From the eleventh to the thirteenth day the animal received 200 cc. of milk by mouth daily. On the twenty-eighth and thirty-first days, 300 cc. of milk was also given by mouth. On the fifty-first day, gastric analysis showed no free acid and a combined acid of 27 points. The weight gradually declined from
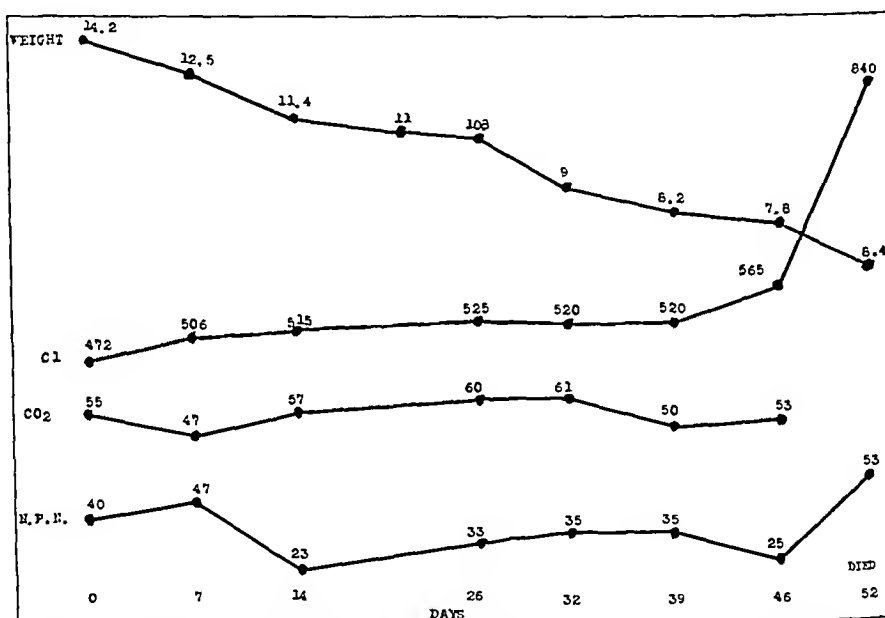
Fig. 4 (dog 533).—Curves of the weight and the figures for the chemical composition of the blood.

14.2 Kg. before operation to 6.4 Kg. on the fifty-second day. This was an average loss of 0.15 Kg., or 1.05 per cent daily of the original body weight. Analyses of the chemical composition of the blood (fig. 4) showed a very slight rise in chlorides during the first thirty-nine days, from 472 to 520 mg. On the forty-sixth day, the chlorides went up somewhat higher, to 565 mg., and on the day of death (fifty-second day) the reading was 840 mg. The carbon dioxide fluctuated only slightly from the preoperative determination of from 55 to 53 mg. on the forty-sixth day. The nonprotein nitrogen was originally 40 mg., but after a slight rise to 47 mg. at the end of the first week it dropped to 23 mg. at the end of the second week. It then fluctuated slightly until the fifty-second day, when it was 53 mg. The behavior of the animal was apparently practically normal until a few days before death, when it appeared to be quite weak. Death occurred on the fifty-second day. At autopsy there was no demonstrable cause of death other than the long-standing obstruction and the severe emaciation from starvation. There was practically no adipose tissue in the subcutaneous, omental, mesenteric or perirenal

regions. The blood count taken at time of death showed a hemoglobin of from 75 to 80 per cent, a red count of 3,050,000 and a white count of 6,400. The urine showed some albumin along with a few red cells and pus cells. The obstructed portion of the bowel measured 95 cm. from the pylorus, and was distended to a diameter of 5.5 cm. in the distal 30 cm. (fig. 5). The wall was enormously hypertrophied in the distal 15 em. In the proximal part in the region of the duodenum the diameter varied from 1.7 to 2 em. The stomach was not distended. The bowel from the jejunostomy opening to the ceeum measured 80 em. in length and varied from 1.2 to 1.8 cm. in diameter.
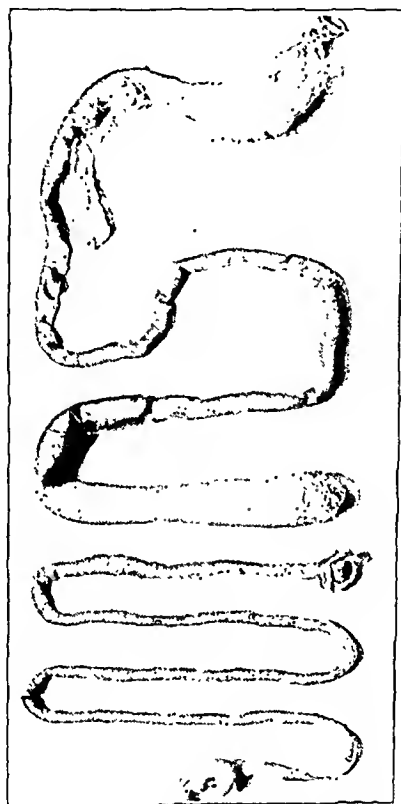
Fig. 5 (dog 533).—Specimen from the dog, which lived fifty-two days. The obstructed bowel measured 95 em.

Dog 575: The obstruction was produced 42 em. from the pylorus. During the first four days the animal received daily an average of 1,350 ee. of 2 per eent sodium chloride. On the fifth day 7 per eent dextrose and 1 per eent sodium chloride solution were started, and approximately 1,200 ee. was given daily in from eight to ten feedings. Vomiting occurred on at least twenty-two of the thirty-eight days of the period of obstruction. On five oceasions a small stool was passed The weight gradually declined from 17.4 to 10 Kg. on the thirty-eighth day, when the animal died. This was an average daily loss of 0.19 Kg., or 1.12 per cent. The chemical composition of the blood showed relatively little change during the obstruction (fig. 6). The blood chlorides were 553 mg. before operation and fluc-
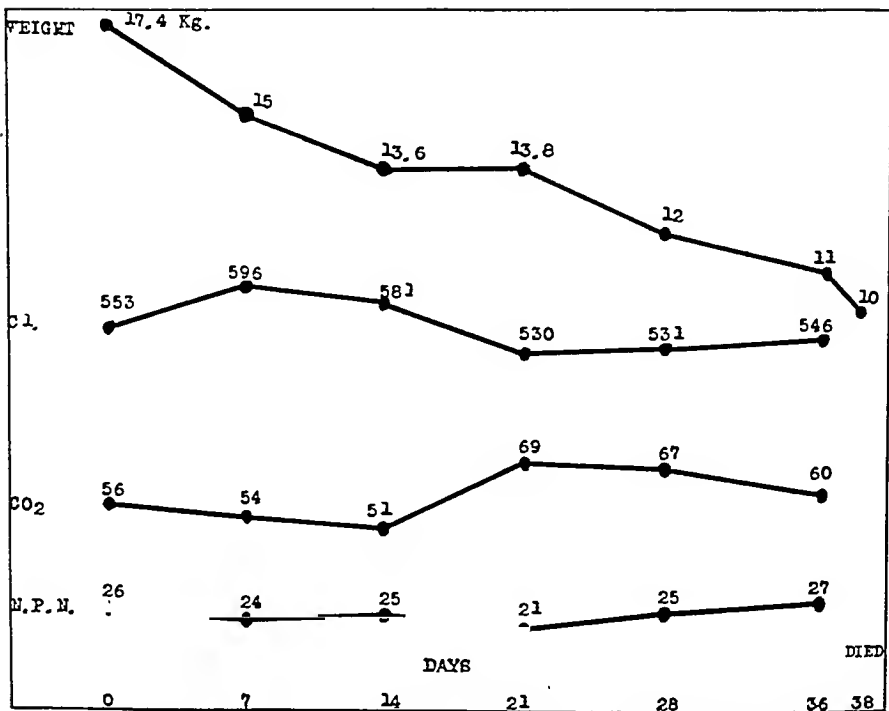
Fig. 6 (dog 575).—Curves of the weight and the figures for the chemical composition of the blood.

Fig. 7 (dog 575).—Specimen from the dog, which lived thirty-eight days. The obstruction was 42 cm. from the pylorus.

tnated slightly up to the thirty-sixth day, when they were 546 mg. The carbon dioxide started at 56 mg. and rose to 69 mg. on the twenty-first day, but came down to 60 mg. on the thirty-sixth day. The nonprotein nitrogen started at 26 mg. and ended at 27 mg. on the thirty-sixth day. The general condition of the animal was good until the thirty-sixth day, when weakness was noticed which became progressively worse until death occurred on the thirty-eighth day. Autopsy revealed a definite bronchopneumonia that was sufficiently extensive to explain completely the immediate cause of death. The stomach and 42 cm. of obstructed bowel were distended (fig. 7). The most marked distention of the bowel was just above the obstruction, where the diameter measured 4 cm. There were 205 cm. of small bowel between the jejunostomy and cecum, which was collapsed.
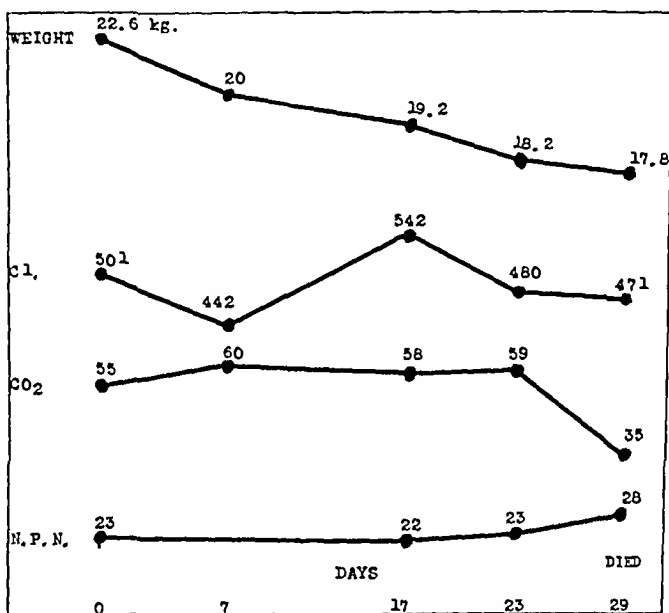
Fig. 8 (dog 664).—Curves of the weight and the figures for the chemical composition of the blood.

Dog 664: In this animal the obstruction was made 50 cm. from the pylorus. About 800 or 1,000 cc. of 1 per cent sodium chloride and 7 per cent dextrose solution was given in from seven to eight feedings daily except for the first two days, when only 2 per cent sodium chloride was used. Vomiting occurred on at least fifteen of the twenty-nine days. The weight declined from 22.6 to 17.8 Kg. This was an average loss of 0.165 Kg. per day, or 0.72 per cent of the original body weight daily. Chemical analysis of the blood showed a change in chlorides from 501 mg. before operation to 471 mg. on the twenty-ninth day (fig. 8). The carbon dioxide started at 55 mg. and stayed at from 58 to 60 mg. until the twenty-third day, and then fell to 35 mg. on the day of death. The blood was taken for chemical determinations two hours before death. The nonprotein nitrogen showed only a slight rise from 23 to 28 mg. The general behavior of the animal was excellent until the twenty-eighth day when it appeared rather weak. On the twenty-ninth day there was a marked change; the animal was spastic and had several convulsions. The animal was unable to stand up, and when molested was seized with convulsions during one

of which it died. At autopsy there was no demonstrable explanation for the cause of death other than the presence of the obstruction. The animal showed little evidence of emaciation as the adipose tissue of the omentum and mesentery was well preserved. There was moderate dilatation of the stomach and 50 cm. of obstructed bowel (fig. 9). The bowel from the jejunostomy to the cecum measured 150 cm.

Dog 99: The obstruction was produced 75 cm. from the pylorus. This animal was given 1,000 cc. of 2 per cent sodium chloride in six feedings daily for the first
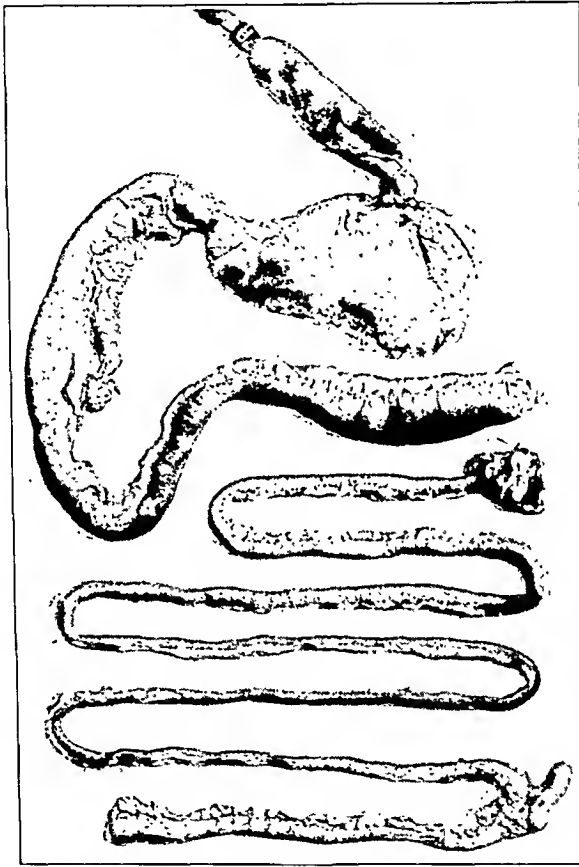
Fig. 9 (dog 664).—Specimen from the dog, which lived twenty-nine days. The obstruction was 50 cm. from the pylorus.

three days. After this 1 per cent sodium chloride and 5 per cent dextrose were used, and the feedings were given nine times a day. The weight gradually fell from 10 to 6.3 Kg. on the twenty-sixth day, when the animal died. This was an average daily loss of 0.127 Kg., or 1.27 per cent. The blood chlorides, which were originally 520 mg., showed relatively little change during the first two weeks; however, on the twenty-sixth day, the reading was 819 mg. (fig. 10). The carbon dioxide fluctuated slightly from 62 mg. before operation to 59 mg. on the twenty-fifth day. The nonprotein nitrogen rose from 25 to 34 mg. on the last day. Vomiting was noticed on at least fourteen days. The animal showed very little premonitory sign of death. Autopsy revealed a leak in the obstructed bowel at the

site of the invaginated stump which had produced a generalized peritonitis. The obstructed bowel was only moderately distended just above the obstruction.

Dog 168: In this animal the obstruction was made 60 cm. from the pylorus. It was given 1,100 cc. of 2 per cent sodium chloride through the jejunostomy opening during the first two days, and thereafter the same amount of 1 per cent sodium chloride and 7 per cent dextrose in from eight to nine feedings daily. The weight declined from 20 to 16.2 Kg. on the twenty-fifth day, when the animal died. For two days previous to death the animal appeared to be definitely spastic. Clinical analysis of the blood showed relatively little change. The chlorides were 482 mg. before operation, and 539 mg. on the twenty-fifth day. The carbon dioxide was 57 mg. before operation and 53 mg. on the last day. The nonprotein nitrogen
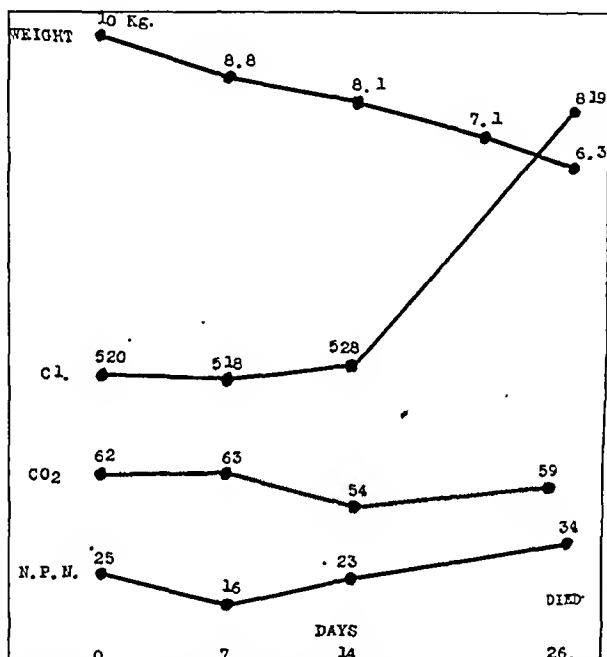
Fig. 10 (dog 99).—Curves of the weight and the figures for the chemical composition of the blood.

changed only from 25 to 27 mg. The last blood was drawn for chemical determinations ten hours before death. Autopsy revealed moderate distention of the obstructed bowel, especially at the distal end. The stomach was not especially distended. There was a patch of bronchopneumonia in the lower lobe of the right lung, which was relatively small. There was some question as to whether this was adequate to explain completely the cause of death.

Dog 170: The obstruction was produced 55 cm. from the pylorus. About 1,200 cc. of 1 per cent sodium chloride and 6 per cent dextrose was given daily in nine feedings. The weight declined from 16.5 to 12.4 Kg. on the twenty-first day, when the animal died. The chemical composition of the blood was determined only up to the fifteenth day. The blood chlorides were 620 mg. before operation, and, after a sharp rise to 826 mg. on the eighth day, fell to 678 mg. on the fifteenth day. The carbon dioxide changed from 61 to 54 mg. and the nonprotein nitrogen rose from 25

to 30 mg. at the end of two weeks. Autopsy showed a marked bronchopneumonia and moderate distention of the obstructed bowel.

Dog. 5: The obstruction was produced 30 cm. from the pylorus. About 900 cc. of 1 per cent sodium chloride and 5 per cent dextrose was given daily in nine feedings. The weight declined from 7.8 Kg. before operation to 5.3 Kg. on the seventeenth day, when the animal died. The blood chemistry taken up to the fourteenth day showed no marked changes. The chlorides rose from 502 to 614 mg.; the carbon dioxide changed from 45 to 48 mg., and the nonprotein nitrogen dropped from 30 to 19 mg. Autopsy showed a rather extensive localized peritonitis about the end

TABLE 1.—*Length of Life and Autopsy Observations in Series of Thirty-Eight Dogs with High Obstruction Treated by Saline Administered into the Jejunostomy Below the Obstruction*

Dog	Length of Life, Days	Autopsy Observations
660	70	Small patch of bronchopneumonia and emaciation
533	52	Emaciation
575	38	Bronchopneumonia
664	29	No findings (unexplained convulsions)
99	26	Generalized peritonitis from leak at obstructed stump
168	25	Small patch of bronchopneumonia
170	21	Bronchopneumonia
5	17	Localized peritonitis about obstructed stump
721	15	Bronchopneumonia (following resuture of wound)
811	13	Bronchopneumonia
655	11	Small patch of bronchopneumonia
577	8	Generalized peritonitis from perforation of bowel
658	8	Bronchopneumonia (following resuture of wound)
893	8	Generalized peritonitis
894	8	Bronchopneumonia
733	7	Generalized peritonitis and bronchopneumonia
83	6	Bronchopneumonia
173	6	Distemper and bronchopneumonia
491	5	Pulled jejunostomy stump out
661	5	Bronchopneumonia
923	5	Pulled jejunostomy stump out
2	4	Pulled jejunostomy stump out
322	4	Distemper (electrocuted)
325	4	Bronchopneumonia
534	4	Pulled jejunostomy stump out
660	4	Generalized peritonitis from perforation of bowel
327	3	Pulled jejunostomy stump out (electrocuted)
425	3	No findings
428	3	No abdominal or chest findings, some edema of brain
490	3	Generalized peritonitis
810	3	Pulled jejunostomy stump out
918	3	Generalized peritonitis
222	2	Bronchopneumonia
225	2	Pulled jejunostomy stump out
326	2	Bronchopneumonia
732	2	Generalized peritonitis
920	2	Bronchopneumonia
921	2	Localized peritonitis and gangrene of jejunostomy loop

of the obstructed stump of the jejunum. There was no definite evidence of a generalized peritonitis.

In addition to the eight animals the protocols of which are given, in thirty other dogs obstructions were produced in the upper jejunum and the animals were treated with sodium chloride and dextrose solution, which was injected into the bowel below the obstruction (table 1). The length of life of the thirty animals not included in the protocol was considerably shortened. One dog died on the fifteenth day, another on the thirteenth and still another on the eleventh. Four died on the eighth day, 1 on the seventh, and two on the sixth. Three died on the fifth day and five on the fourth. Six animals died on the third day, and another six on the second day. In this series of thirty animals the autopsy observations were pulmonary infection, thirteen; peritoneal infection, seven; pulling out of jejunostomy

stump and evisceration, seven; pulmonary and peritoneal infection, one. In two the observations were not adequate to explain death, and in one, listed under pulmonary infection, the patch of bronchopneumonia was relatively small and did not appear sufficiently extensive completely to explain death.

Series II: Treated with Distilled Water Introduced into the Jejunostomy Opening (control).

In a series of four animals an obstruction was produced in the upper jejunum in the same manner as in the previous series. The dogs were given approximately 1,000 cc. of distilled water daily through the jejunostomy opening in from eight to nine feedings. Nothing was given by mouth. The dogs lived five, six, eight and eleven days. The changes in the chemical composition of the blood were rather slight in the animals that lived five and six days; however, marked changes were observed in the two that lived eight and eleven days (table 2). The most noticeable change was seen in dog 190, in which the blood chlorides fell to 212 mg., the

TABLE 2.—*The Weight, Chemical Composition of the Blood, Time of Death and Length of Obstructed Bowel in Water Control Series*

				Chemical Composition of the Blood			
	Lived	Weight	Distance of Obstruction From Pylorus	Day	Chloride, Mg.	Carbon Dioxide, Mg.	Nonprotein Nitrogen, Mg.
Dog 76..........	5 days	21 Kg.	50 cm.	0	450	47	32
				3	419	49	45
Dog 189.........	6 days	17 Kg.	45 cm.	0	495	49	23
				3	465	53	23
				5	416	57	28
Dog 657..	8 days	13 Kg.	45 cm.	0	528	54	33
				2	495	48	23
				5	407	64	31
				7	317	71	92
				8	288	52	133
Dog 190..	11 days	16 Kg.	45 cm.	0	447	50	33
				3	384	57	38
				5	341	70	37
				7	291	79	51
				9	242	80	80
				10	212	84	118

carbon dioxide rose to 84 mg., and the nonprotein nitrogen rose to 118 mg. At autopsy there were no demonstrable observations other than the obstruction to explain death.

COMMENT

The marked prolongation of life in high obstruction that was obtained in this experiment with relatively slight changes in the chemical composition of the blood was apparently due primarily to the replacement, in the form of sodium chloride solution, of the water and important blood electrolytes, fixed base (chiefly sodium) and chloride ions, which were lost in the vomited digestive secretions; secondarily to the addition of nutritive material which helped to ward off starvation: dextrose, plus peptonized milk in one instance. The blood chlorides remained at a normal level in all the obstructed animals except three (dogs 533, 99 and 170), in which there was a marked rise. In the experiments of Gatch, Trusler and Ayres[2] several instances of

a rise in blood chlorides were observed when the animals in which obstructions were produced were treated by sodium chloride solution subcutaneously or intravenously. One animal with a low ileal obstruction, which received 1.8 per cent sodium chloride subcutaneously in from 1,000 to 2,000 cc. amounts daily and died on the twenty-first day, had a terminal blood (sodium) chloride of 830 mg. Another animal with a duodenal obstruction, which received 30 cc. of 33 per cent sodium chloride solution intravenously daily, died on the third day with a blood (sodium) chloride of 724 mg. Denis and Sisson[28] were able to produce a rise of 18 per cent in the blood chlorides of goats after the ingestion of large amounts of sodium chloride by mouth. It is possible that the high blood chlorides that were observed in three instances in this experiment were due to the administration of more sodium chloride than was actually needed by the animal to replace the lost electrolytes.

The replacement of water without the blood electrolytes does not delay the usual rapid death or prevent entirely the characteristic chemical changes of the blood in high obstruction. The dogs in the water control series died in five, six, eight and eleven days, and marked changes were observed in the blood chemistry of the two that survived the longest. In the experiments of Saito, Sakai and Suzuki[29] an animal with an obstruction of the duodenum was treated by instilling 1,000 cc. of water daily into the bowel below the obstruction. This animal lived two days and showed a fall in the blood chlorides from 517 to 337 mg., and a rise in nonprotein nitrogen from 40 to 250 mg. Matsukura[25] also had an animal that lived two days after the same procedure. In this instance the blood chlorides fell from 516 to 292 mg. Haden and Orr[9] found that distilled water injected subcutaneously into animals with an obstruction caused death even more rapidly than it occurred in untreated animals. Gatch, Trusler and Ayres[1] observed this also, but further found that animals without obstruction also died following the injection of distilled water.

Gatch, Trusler and Ayres[1] found that the intravenous injection of concentrated sodium chloride solution prevented a marked fall in the blood chlorides in obstruction but did not appreciably delay death. Haden and Orr also found that concentrated sodium chloride solution restored the blood chlorides to normal, but they felt that it had a definitely beneficial effect in the recovery of animals in which obstruction had been produced when the obstruction was subsequently relieved by a second operation. Nevertheless, they did not report any instances

28. Denis, W., and Sisson, W. R.: A Study of the Chlorine Content of Milk and Blood After Ingestion of Sodium Chloride, J. Biol. Chem. **46**:483, 1921.

29. Saito, S.; Sakai, K., and Suzuki, S.: Further Studies on Acute Intestinal Obstruction, Jap. J. M. Sc. (Tr. Surg. Orth. & Odont.) **1**:43, 1927.

of marked prolongation of life by injections of concentrated salt solution as they did with injections of diluted solutions. Haden and Orr [10] further demonstrated that the injection of other chloride salts, such as ammonium, potassium, calcium or magnesium chloride, did not prevent the usual fall in blood chlorides or delay the fatal outcome. Neither did numerous other salts, such as iodides, sodium bromide, sodium sulphate, magnesium sulphate, sodium citrate, monosodium phosphate and disodium phosphate, have any beneficial effect in preventing the chemical changes in the blood or in delaying death.

It appears that there are two important primary factors necessary to prolong life in high obstruction: replacement of water and replacement of the blood electrolytes by sodium chloride salt. The replacement of one without the other appears to have relatively little value, because the dehydration that occurs in obstruction is due not only to the loss of water, but also to the loss of the blood electrolytes that the body needs to hold water, even if it is replaced.

In regard to the effect of dextrose, it appears that its value is only nutritive. Haden and Orr [8] found that there was no demonstrable beneficial effect in preventing the changes in the chemical composition of the blood or in delaying death from the administration of dextrose solution subcutaneously to an animal with an obstruction. Saito, Sakai and Suzuki [29] introduced 1,000 cc. of 5 per cent dextrose daily into the bowel below the point of a duodenal obstruction. Their animal lived six and one-half days and showed a fall in the blood chlorides from 495 to 238 mg. and a rise in nonprotein nitrogen from 20 to 40 mg. In the experiments of Matsukura,[25] a similarly obstructed and treated animal lived four days and showed a fall in blood chlorides from 495 to 305 mg. It appears that dextrose solution may replace water, but this without the blood electrolytes is valueless and the dextrose itself has no beneficial effect except as a nutritive agent. The 50 to 70 Gm. of dextrose given to the animals daily in this experiment offers from 200 to 280 calories a day that would not otherwise be available. In the instance of the animal given peptonized milk, this added calories to the diet and helped the state of nutrition by its protein content, although it was probably not all sufficiently split to permit complete absorption in the bowel.

The loss of weight observed in the animals in this experiment varied considerably. The daily average loss varied from 0.0771 to 0.195 Kg., and the daily loss calculated in percentage of the original body weight varied from 0.642 to 1.88 per cent. In an experiment by Kunde,[30] a series of three animals that were simply starved for from thirty-seven

30. Kunde, M. M.: The After Effect of Prolonged Fasting on the Basal Metabolic Rate, J. Metab. Research **3**:399, 1923.

to forty-one days, the loss of weight averaged 0.117 Kg., or 1.01 per cent, per day. The effect of the dextrose was apparently not very great and in some instances valueless in preventing loss of weight from the starvation of obstruction. In the animal that Armour and his associates [26] kept alive for fifty days, the loss of weight was 0.71 per cent of the original body weight daily, which compares favorably with two of the animals in our series (dogs 168 and 664). A more complete diet was used in Armour's experiment than was used in any of our animals. In the dog that we kept for seventy days, the loss of weight was the least, 0.071 Kg., or 0.642 per cent, daily. The maximum beneficial effect of the nutritive material in our experiment and in Armour's has been to prevent approximately a third of the daily loss of weight that occurs from starvation alone.

The death that ultimately results was found to be definitely due to a complication in most of the animals. This is not surprising when one considers that the resistance of the animals is probably markedly lower to infections, especially pulmonary, as a result of the starvation alone, which is only partially combated by the administration of nutritive material in this experiment, which at best would not have been adequate to maintain a balanced state of nutrition. In one animal (dog 575) that lived twenty-nine days the explanation for the cause of death was obscure. There was no alteration in the blood chlorides or nonprotein nitrogen just before death; however, there was marked acidosis. The premonitory symptoms were those of spasticity and convulsions. The anatomic observations revealed nothing to explain death satisfactorily. The general state of nutrition of the animal was apparently good, because the mesenteric and omental adipose tissue was well preserved. It is not easy to say whether the acidosis was responsible for the convulsions or was merely another evidence of a profound metabolic disorder. Another animal (dog 169) behaved similarly toward the end, and a patch of bronchopneumonia was found at autopsy which did not seem adequate completely to explain death because of its small size. The chemical composition of the blood was practically the same on the day of death as before operation. Kunde [30] described marked manifestations of the central nervous system in one of three animals that were starved longer than a month. It is possible that death in the two animals in this experiment, which showed marked nervous manifestations just before, may have been due to a metabolic disorder of nutrition from deficiency in some organic or inorganic substance necessary for life. This may have been accidentally supplied to the other animals that lived longer, because most of the other animals occasionally had some food by mouth. After about a month on an artificial diet of sodium chloride and dextrose, this factor may become important. In

the series of thirty-eight animals in which obstructions were produced and the animals treated with saline and dextrose, there were two that died in three days without any demonstrable changes at autopsy other than the presence of the obstruction which would adequately explain death. These animals were operated on during a very hot spell of weather, and it is possible that heat prostration may have had something to do with the early death. On the other hand, death may have been due to the obstruction even though the dogs were receiving sodium chloride the same as the other animals. This, of course, opens the question as to whether or not there is a factor in death from high obstruction other than the loss of digestive secretions which under some circumstances may kill the animal even if the constituents of the lost secretions are replaced. This factor may have been responsible for the death of other animals (dogs 575, 168, 655 and 5). One of these (dog 5) died on the seventeenth day, showing only an area of localized peritonitis about the obstructed stump. The animal that lived fifty-two days (dog 533) showed a marked hyperchloremia on the day of death. There was no demonstrable complication found at autopsy, and the only explanation that can be offered other than the presence of the obstruction was profound emaciation from loss of over half its original body weight. The animal that lived seventy days (dog 660) showed only a small patch of bronchopneumonia and marked emaciation from the long-standing obstruction with inadequate nutrition.

The clinical application of the evidence that has been presented that an important factor in death from high obstruction is the loss of the digestive secretions depends to a large extent on the individual case. Uncomplicated high obstruction does not occur frequently. The more usual picture is that of an obstruction lower in the intestinal tract or complicated by some necrosis of the bowel from strangulation or distention. Loss of digestive secretions occurs in varying degrees in the latter case, depending largely on the length of bowel above the obstruction that would afford an absorbing surface for the secretions. In many cases of this type toxemia may be the more important factor in causing death and may overshadow the rôle of the loss of digestive secretions, as suggested by Gatch and his co-workers.[1] The beneficial effect of the administration of saline probably depends on the degree to which the body has been depleted of fluid and blood electrolytes. This depletion is a much more outstanding feature in uncomplicated high obstruction than it is in low obstruction or occlusion with damage to the bowel. Hence the improvement following the administration of saline before surgical intervention would be expected to be in proportion to the importance of the factor of loss of digestive secretions. It is not likely that the saline appreciably influences the toxemia, and if

this is of importance in the particular case its beneficial effect in replacing the lost digestive secretions would probably be masked to some extent. It appears to us that the rational stand to take in regard to saline therapy is to advocate replacement of as much fluid and blood electrolytes as is reasonably possible before operation by large amounts of physiologic solution of sodium chloride or Ringer's solution given subcutaneously or intravenously when it appears that there has been a considerable loss of digestive secretions. Furthermore, any prolonged delay to permit extensive preoperative saline therapy does not seem justifiable, particularly because of the difficulty in determining the importance of the factor of toxemia and especially in predicting whether the obstruction is complicated by necrosis of the bowel, which would be benefited only by early operation and not by the saline. If the clinician is reasonably sure that the outstanding factor in a case of uncomplicated high obstruction is loss of digestive secretions, then resort to a more prolonged and extensive saline therapy before operation may be justified.

SUMMARY

When animals in which a high intestinal obstruction had been produced were treated by giving them about a liter daily of 1 per cent sodium chloride and from 5 to 7 per cent dextrose solution plus, in one instance, peptonized milk by a jejunostomy opening in the bowel below the obstruction, two survived fifty-two and seventy days, six others lived from seventeen to thirty-eight days, and thirty died between the second and fifteenth day. The animals that survived for the long periods showed no evidence of any so-called "toxic" symptoms. Vomiting occurred about every other day. Watery stools were sometimes passed when the dextrose was poorly tolerated, and occasionally a small solid stool. The weight showed a gradual decline, varying from a daily loss of 0.0771 to 0.195 Kg., or from 0.642 to 1.88 per cent of the original body weight. The total loss of weight was over half the original body weight for the animal that lived fifty-two days, and almost half for the animal that lived seventy days. Chemical studies of the blood showed that the chlorides remained at a normal level during the entire period of obstruction except in three instances, when the figures were much higher than normal. The carbon dioxide remained normal except in one instance, when it decreased on the day of death. The nonprotein nitrogen showed relatively little change, except an occasional slight rise. At autopsy the stomach and obstructed bowel were found to be moderately distended. There was a considerable thickening of the wall of the bowel just above the obstruction in animals that survived for long periods. The immediate cause of death was definitely due to a complication, either pulmonary or abdominal, in most

of the animals. In the two animals that survived fifty-two and seventy days, the outstanding feature was marked emaciation. In a series of four dogs with high intestinal obstruction, distilled water was administered through the jejunostomy opening. These animals died in five, six, eight and eleven days, without any postmortem changes other than the obstruction. Chemical analysis of the blood of the two dogs that lived eight and eleven days showed the usual changes of untreated animals with obstructions.

CONCLUSIONS

1. In high intestinal obstruction an important factor in the cause of death is the loss of digestive secretions. This view is supported by observations in this experiment in which some animals lived from fifty-two to seventy days with a high obstruction. The rôle of the sodium chloride solution, which was administered daily through a jejunostomy opening below the obstruction, was to replace the water and important blood electrolytes, fixed base (chiefly sodium) and chloride ions, which are ordinarily lost from failure of resorption and vomiting.

2. In regard to obstruction low in the intestinal tract or complicated by necrosis of the bowel, the loss of digestive secretions may be a factor in the cause of death, but this is of varying importance, depending on the length of bowel above the obstruction which would offer opportunity for some resorption of the secretions. It is in this group tha toxemia probably plays the more important rôle, and in man operative treatment should be resorted to immediately.

3. The beneficial effect of the administration (subcutaneously or intravenously) of saline solutions clinically in cases of intestinal obstruction appears to depend largely on the extent to which the body has suffered from the loss of digestive secretions from failure of resorption and vomiting. When toxemia is a conspicuous factor, its benefit may be masked to some extent.

ADDENDA

Since submitting this article for publication, we have kept an animal with a high intestinal obstruction alive for eighty days. This dog also was treated by the injection of a saline and dextrose solution into the bowel below the obstruction, but in addition intestinal contents obtained from an animal with an intestinal fistula were given. Autopsy showed bronchopneumonia.

Benedict, Stewart and Cutner [31] reported that they kept an animal with high obstruction alive for fifty-eight days by administering a liter or more of physiologic solution of sodium chloride daily in the bowel below the obstruction.

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31. Benedict, E. B.; Stewart, C. P., and Cutner, P. N.: The rôle of Bile in High Intestinal Obstruction, Surg., Gynec. & Obst. **54**:605 (April) 1932.

BREAKING STRENGTH OF HEALING FRACTURED FIBULAE OF RATS

VI. OBSERVATIONS ON THE INFLUENCE OF BILATERAL OVARIECTOMY

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The ovaries of the female are concerned not only with the regenerative functions of the animal, but also to no small extent with its metabolism in general. The influence exerted by the ovaries on the growth and repair of bone is incompletely understood, and little work has been done on this aspect of the problem. For this reason we decided to determine the effect of bilateral ovariectomy on the breaking strength of fractured and unfractured fibulae of rats.

Marsiglia,[1] estimating the process of calcification in fractured bones by means of roentgenograms, was unable to demonstrate that extirpation of the ovaries influenced the formation of the callus. Reach[2] found a slight reduction in the calcium oxide content of the skeleton of mice following the removal of the ovaries, and Korenchevsky[3] was unable to find any essential difference by chemical or histologic examination in the skeletons of growing rats after ovariectomy. On the contrary, Poncet,[4] Selheim,[5] Pirsche[6] and Tschirvinsky[7] found that the growth of the epiphysis continued beyond the normal limits after castration. Selheim particularly demonstrated this effect in dogs. In

1. Marsiglia, G.: Arch. ital. di chir. **5:**197, 1922.

2. Reach, F.: Biochem. Ztschr. **42:**59, 1912.

3. Korenchevsky, V.: J. Path. & Bact. **26:**207, 1923.

4. Poncet, A.: De l'influence de la castration sur le développement du squelette, Compt. rend. Soc. de biol. **55:**65, 1903.

5. Selheim, H.: Centralbl. f. Gynäk. **77:**203, 1899.

6. Pirsche, E.: De l'influence de la castration sur le développement du squelette, Recherches cliniques et expérimentales, Thesis, Lyon, 1902, no. 77.

7. Tschirvinsky, N.: Arch. f. mikr. Anat. **75:**522, 1910.

osteomalacia, controversy has existed for a long time as to the beneficial results of ovariectomy. Fehling,[8] for one, showed that the disease was markedly benefited by the removal of the ovaries, and Goldthwait and his associates,[9] in an interesting case report, reported a positive calcium balance in a patient with osteomalacia following ovariectomy. It is, however, not to be forgotten that the interdependency of the glands of internal secretion make it extremely difficult, if not at present impossible, to attribute particular disease phenomena entirely to one gland.

PROCEDURE

Young female rats weighing from 150 to 190 Gm. were selected for study. After they were on a standard diet[10] for one week, a bilateral ovariectomy was performed on half of the forty animals used in the experiment. In all forty the right fibula was fractured by the method described before,[11] and the animals returned to their cages. On the ninth postoperative day five of the rats with ovariectomies, and five with fractured fibulae only, were killed. This procedure was repeated on the fifteenth, twenty-first, twenty-seventh and thirtieth postoperative days. Their fractured right and unfractured left fibulae were then prepared as described elsewhere,[11] and the breaking strengths determined. In addition, the relative body weights of the rats, the amounts of the ration they consumed and the roentgenographic appearance of their calluses at different days of healing were determined.

RESULTS

To avoid confusion, those rats with bilateral oophorectomies, as well as fractured right fibulae, have been designated the ovariectomy fractured group, while those with only fractured right fibulae, and without ovariectomies, are called the ovariectomy control group.

The Breaking Strengths of the Fibulae: For the Ovariectomy Fractured Group.—The breaking strength ratios, the details for the calculation of which have been given in a former paper,[11] were used throughout this study.

The fractured right fibulae in these animals had a ratio of 38 on the ninth day of healing. By the fifteenth day the ratio had risen slightly to 82, and on the twenty-first day it was 128. The highest point reached was gained on the twenty-seventh day, when a ratio of 207 was found. The ratio for the final and last observation on the thirtieth day was 143.

8. Fehling, H.: Arch. f. Gynäk. **34**:171, 1891.

9. Goldthwait, J.; Painter, C.; Osgood, R., and McCrudden, F.: Am. J. Physiol. **14**:389, 1905.

10. Moise, T. S., and Smith, A. H.: J. Exper. Med. **40**:13, 1924.

11. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Howes, E. L.: The Breaking Strength of Healing Fractured Fibulae of Rats: II. Observations on a Standard Diet, Arch. Surg. **24**:458 (March) 1932.

The unfractured left fibulae began on the ninth day with a ratio of 165, which had increased to 241 by the fifteenth day, but thereafter fell on the twenty-first day to 193. The ratio on the twenty-seventh day was 299, and on the thirtieth day 255.

When the foregoing results were charted, it was seen that the healing strength of the fractured right fibula rose in almost a straight line to the twenty-seventh day. In earlier experiments we found that the strength of the callus increased to the fifteenth day, when the primary callus was considered to have been formed, and that from the fifteenth to the twenty-first day there was an abrupt loss in the healing strength, which was felt to be largely due to the rapid development of the medullary cavity at that time.[12] We found no such peak on the fifteenth day in the rats with bilateral oophorectomies, but did observe a peak on the twenty-seventh day. Nor did we note a secondary drop in strength in the callus between the fifteenth and twenty-first days as

TABLE 1.—*Breaking Force and Ratio of Fractured and Unfractured Fibulae of Ovariectomy Fractured Group* *

Postoperative Days	Ratio for Unfractured Left Fibulae	Ratio for Fractured Right Fibulae
9	165	38
15	241	82
21	193	128
27	299	207
30	255	143

* Refer to table 1n for complete data.

we had in former work. There was, however, a drop in the strength of the fracture in the ovariectomized animals after the twenty-seventh day, which we do not believe to be of the same significance as the secondary drop normally occurring earlier (fig. 1).

The strength of the unfractured left fibulae in this group of animals varied in a manner closely resembling that found to characterize the left fibulae on other diets.[12] Ordinarily we have come to expect that the strength of the left fibula rises and falls when the strength of the right fibula rises and falls. As the strength of the fracture increases, at first the strength of the unfractured left fibula has also been found to grow greater. The right naturally increases more rapidly, but both rise simultaneously. When the right normally loses strength between the fifteenth and twenty-first days, the left likewise diminishes, but in this case at a more rapid rate than the right. However, here we find the left showing independently the type of breaking

12. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Lumsden, R. W.: Breaking Strength of Healing Fractured Fibulae of Rats: III. Observations on a High Fat Diet, Arch. Surg. **25**:467 (Sept.) 1932.

strength curve we have come to expect, while the right, on the contrary, was seen to increase without variation until it reached the twenty-seventh day. Evidently the removal of the ovaries has more effect on the fractured than it does on the unfractured fibula.

For the Ovariectomy Control Group.—The fractured right fibulae in the control group had a breaking strength ratio on the ninth post-operative day of 77. On the fifteenth day the ratio had risen to a peak, such as was found elsewhere to be one normally occurring at that time,[11] and had a ratio of 155. The ratio thereafter fell, as it
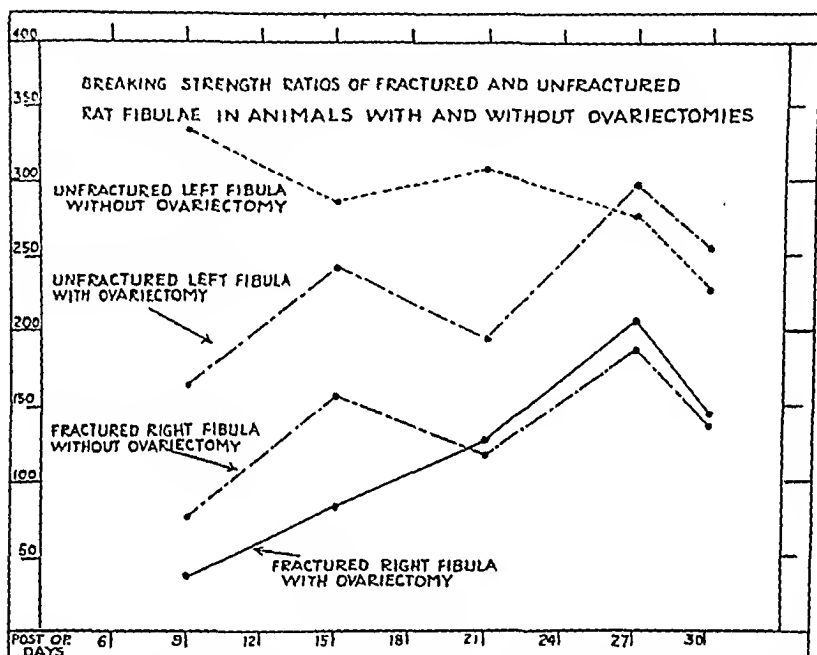
Fig. 1.—The ovariectomized rats showed a characteristic breaking strength curve for the left fibula. The right fibula was atypical, since the secondary drop in healing strength did not develop between the fifteenth and twenty-first days. The control rats with their ovaries intact showed a persistent reduction in the strength of their left fibula. That of the right fibula, however, rose and fell as we normally expect it to. Usually that of the left rises and falls simultaneously with the right. Consequently, we felt the metabolism of the control rats to be inadequate in maintaining the normal strength relationship between the two fibulae.

theoretically should, to 119 on the twenty-first day. On the twenty-seventh day it rose once more to reach a ratio of 189. At the last observation the ratio was 136.

The unfractured left fibulae in the controls began on the ninth day with a ratio of 333, which by the fifteenth day had fallen to 286. Thereafter it was found to be 309 on the twenty-first day, 278 on the twenty-seventh day and 239 on the thirtieth day (fig. 1).

The fractured right fibulae in the control group showed a closer resemblance to normal than did the fractured right fibulae of the ovariectomized rats. This was expected, as the control rats were ostensibly normal animals. The differences found between the fractured right fibulae of the control group in this paper, and the normal fractured right fibulae as established in a former contribution,[11] lie primarily in the height of the ratio attained. The character of the curves was the same for the two, but the control rats did not possess the strength of the normals.

The unfractured left fibulae in the control group did not resemble the normal as much as did the left fibulae of the ovariectomized rats. The changes in the fibular strength of the control left fibulae were not seen to take place simultaneously with rises and falls in the strength of its fractured right fibulae. On the contrary, the strength of the unfractured left fibulae in the control group fell throughout the experi-

TABLE 2.—*Breaking Force and Ratio of Fractured and Unfractured Fibulae of Ovariectomy Control Group* *

Postoperative Days	Ratio for Unfractured Left Fibulae	Ratio for Fractured Right Fibulae
9	333	77
15	256	153
21	300	119
27	278	159
30	239	186

* Refer to table 2a for complete data.

ment. We have already noted that the strength of the left fibulae in those animals with their ovaries removed fluctuated in a characteristic manner, but the plotted ratios in figure 1 show no such variations in strength for the control left fibulae. The explanation of this is apparently concerned in the metabolism of the control group. As will be shown later, the control rats lost weight consistently, and we have found elsewhere that the weight of the animal exerts a decided influence on the strength of its fibulae.[11]

Relative Studies on Animal Weights and Food Consumption: For the Ovariectomy Fractured Group.—The body weights of this group fell from the ninth to the twenty-first postoperative days, when they again became normal (table 3). Subsequently the weights decreased at a rapid rate to the twenty-seventh day, after which the previous loss was somewhat regained, and the final weighings on the thirtieth day were not greatly below normal (fig. 2).

The food consumed by the ovariectomized group remained relatively constant until the twenty-first day was reached, when a definite increase in the quantity of the diet ingested took place. Thereafter the quantity was about the same as that taken by the control rats (table 3 and fig. 2).

The weights of the ovariectomized rats were greater than those of the control group. This is in at least partial agreement with common opinion that an increase in body weight follows extirpation of the ovaries. Concomitantly, the quantity of food ingested by the oophorectomized animals was slightly more than that taken by the control rats.

For the Ovariectomy Control Group.—The body weights of this group were lower throughout than those of the ovariectomized animals, except for the twenty-seventh day when they were slightly higher (table 4). There is reason to believe that the metabolism of the control rats was insufficient to maintain the characteristic rise and fall in the
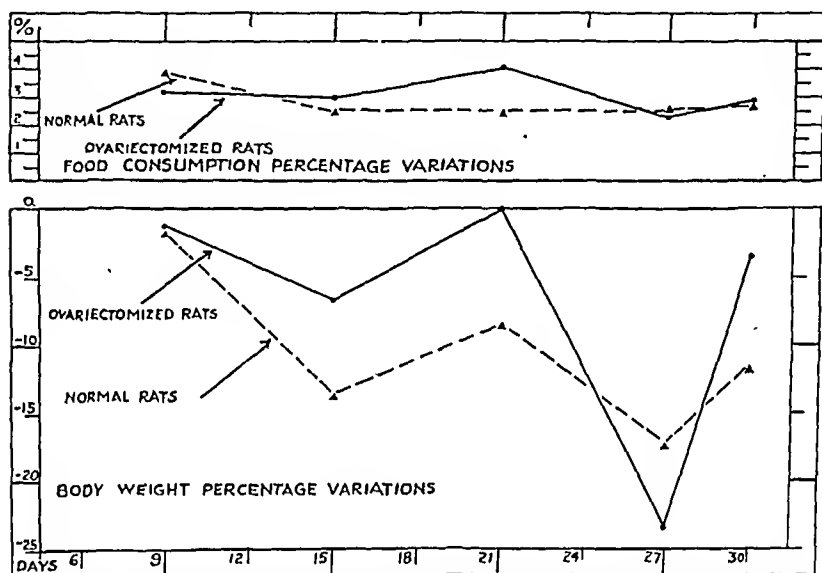
Fig. 2.—Body weight plotted as percentage difference in body weight from operation to death, and food consumption plotted as percentage body weight at operation.

strength of the unfractured left fibulae such as had been found to be the normal occurrence in unfractured left fibulae with animals in which be the normal occurrence in unfractured left fibula with animals in whom the right fibula was fractured.[11] This failure of the unfractured left fibulae in the control lot to approach the normal findings, despite the fact that the fractured right fibulae in the same group did resemble the normal fractured right fibulae, may mean that the metabolism was insufficient to prevent the fractured right from withdrawing from the unfractured left fibulae those elements of healing strength, probably largely calcium and phosphorus salts, which the metabolism of the rats was unable to furnish from the diet as it had been in the group formerly reported.[11]

The food consumed by the control rats was slightly less than that taken by the ovariectomized rats (table 4 and fig. 2). The difference was so little, however, that it was comparatively insignificant. Evidently, although the ovariectomized and control rats ate nearly the same amount of their ration, the ovariectomized group was better able to maintain weight than the controls. This may be further evidence of the abnormal metabolism of the controls, or on the other hand it may be but evidence of the reduced metabolism of the ovariectomized lot. The latter is probably the more likely of the two. However, when we compared the weights of the control group with those reported for the

TABLE 3.—*Summary of Body Weights and Food Consumption of Ovariectomy Fractured Group* *

Postoperative Days	Difference in Weight from Operation to Death as per Cent of Body Weight at Operation	Food Consumed per Day from Operation to Death as per Cent of Body Weight at Operation
9	— 0.6	3.2
15	— 6.3	3.0
21	0.0	4.1
27	—23.2	2.4
30	— 3.5	2.9

* Refer to table 3a for complete data.

TABLE 4.—*Summary of Body Weights and Food Consumption of Ovariectomy Control Group* *

Postoperative Days	Difference in Weight from Operation to Death as per Cent of Body Weight at Operation	Food Consumed per Day from Operation to Death as per Cent of Body Weight at Operation
9	— 1.7	3.9
15	—13.6	2.6
21	— 8.3	2.6
27	—17.1	2.6
30	—11.3	2.8

* Refer to table 4a for complete data.

standard diet group in a former paper [11] it was apparent at once that the weights of the controls, in the light of the earlier work, were not normal. In the standard diet group we had found body weight maintained above normal until the eighteenth day, with a slight drop below normal on the twenty-first day, and a point on the thirtieth day decidedly above the original weight at the onset of the experiment. Nothing resembling this was found on the weights of the ovariectomy controls. They fell from the beginning to the end of the study. Consequently, it is quite likely that these control rats were metabolically subnormal, which would account to no small extent for the variation from the normal found in their fibular breaking strength.

ROENTGENOGRAPHIC STUDIES OF REPRESENTATIVE FRACTURES

Of the Ovariectomized Rats.—The calcification of the callus in these fractures was observed to be retarded (fig. 3). The density of the callus was appreciably less on the ninth, fifteenth and twenty-first days than it was in the controls. A poorly selected roentgenogram of the twenty-seventh day control fracture made a comparison on that day
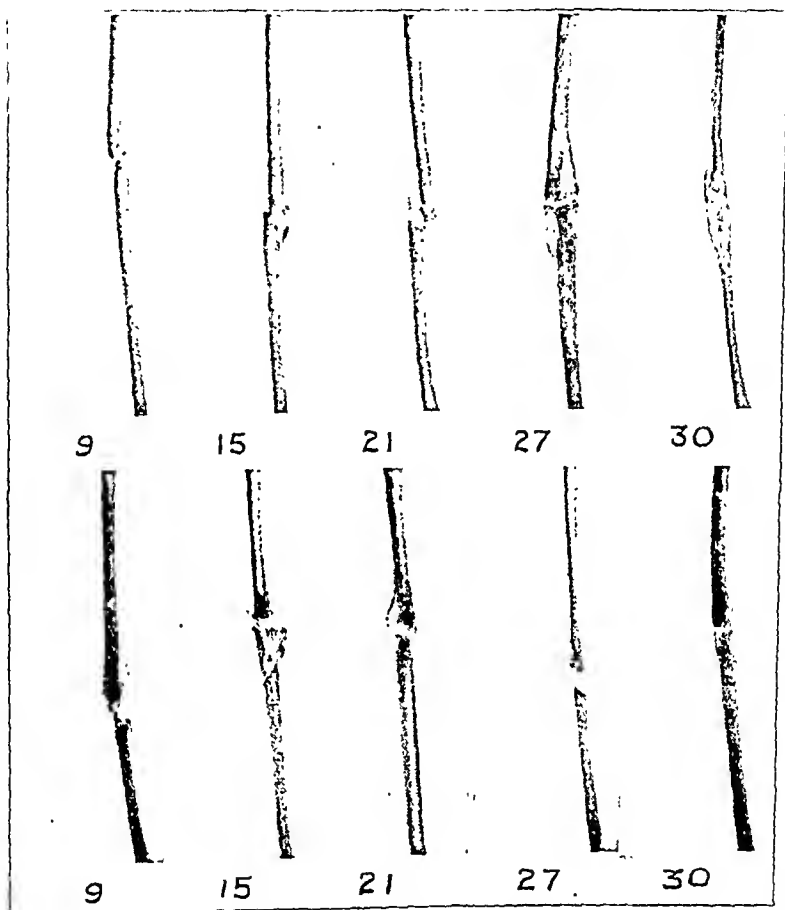
Fig. 3.—Representative roentgenograms at different postoperative intervals. The upper section of roentgenograms shows the fractured right fibulae of ovariectomized rats; the lower section, the fractured right fibulae of normal female rats. With the exception of the twenty-seventh day fracture, the controls appear to possesss more calcific material, and consequently more strength, than the calluses of the ovariectomized rats. Prior to the twenty-first day this evidently was true, but later it is questionable. Due to the lack of agreement between the roentgenograms and the breaking strengths, we have come to believe the roentgenogram an inadequate index of healing strength.

impossible. On the thirtieth day, however, the ovariectomized rat still showed less calcium deposited in its fracture than was noted in the control callus.

Of the Ovariectomy Controls.—Calcification of the healing fracture progressed at a normal rate in the ovariectomy controls (fig. 3). In that respect they so closely resembled the standard diet fracture series described before [11] that no attempt will be made to consider them further.

<div align="center">COMMENT</div>

The healing strength of fractured fibulae of rats on whom bilateral oophorectomies had been performed was below that of their controls until the twenty-first day postoperatively. Subsequently the healing strength was slightly greater. By roentgenographic examination it appeared that in large part the early diminution in strength was due to a delay in the process of calcification of the primary callus. The delay may possibly have been due to the production of a negative calcium balance, which, however, is not in accord with the findings of others on osteomalacia where a positive calcium balance with an increase in the density of the bones of the body was said to have followed extirpation of the ovaries.[13] It is not to be forgotten that in cases of parathyroidectomy the calcium of the blood stream is increased, and yet it has not been satisfactorily demonstrated that fractures heal the quicker as a result of such an elevation. Evidently the form in which the calcium exists in the blood stream is of as much, if not more, importance than is a quantitative increase. Furthermore there is a question as to whether one may compare osteomalacia and a fracture in respect to their effects on calcium metabolism in rats.

The metabolism of ovariectomized rats is by far too large for us to attempt, or even to desire, to create the impression that removal of the ovaries in female rats will of itself slow up the healing of fractures by inhibiting the deposition of calcium salts. We shall show at a later date that orchidectomy, and possibly thyroidectomy, and parathyroidectomy will produce a similar reduction in the healing strength of fractured rat fibulae. The metabolism of the salts utilized in the repair of bone is so intimately bound up with many of the glands of internal secretion that as yet no particular one is definitely known to control the entire picture.

The body weights of the ovariectomized rats did not show an absolute gain. Rather one may say their weights were more completely maintained than were those of the controls, yet the weights were never greater than normal, or more correctly greater than the original weight

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13. Fehling;[8] Goldthwait, Painter, Osgood and McCrudden.[9]

at the beginning of the experiment. The influence of castration has been investigated in the human female by Geist and Goldberger,[14] who found that at best a slight increase in body weight followed oophorectomy. At the same time there was a very moderate drop in the basal metabolic rate, while the blood chemistry changed but little, if at all. It would seem possible that in the ovariectomized rats the better maintenance of body weight might in part be explicable by a reduction in the metabolism along with a somewhat greater consumption of food.

CONCLUSION

Female albino rats with fractured right fibulae, and bilateral oophorectomies, had less strength in their healing callus for the first twenty-one days of healing than did their controls in which the ovaries were not removed, but which also had had their right fibulae fractured. Later the strength of the calluses in the ovariectomized rats was slightly greater than that of the control calluses.

The formation of the primary callus in ovariectomized rats during the first twenty-one days of the reparative process would seem to be more influenced than were the later stages in the repair of the fracture. The findings on the breaking strength machine were substantiated in part by similar findings on roentgenographic examination. Roentgenographic studies of selected fractures over the observed intervals strongly suggested a retardation in the calcification of the provisional callus.

The better maintenance of body weight in the ovariectomized group than in their controls was in agreement with similar findings by other workers.

ADDENDA

COMPLETE DATA ON OVARIECTOMIZED RATS

Table 1a.—*Breaking Strength and Ratio for Fractured Right and Unfractured Left Fibulae of Ovariectomy Fractured Group*

Postoperative Days	Rat No.	Weight (W)		Force (F)		Ratio (R)	
		Operation	$(10.W)^{2/3}$	Left	Right	Left	Right
9	3081	178	146.9	250	..	170	0
	3082	170	142.5	260	90	182	63
	3083	172	143.6	280	50	195	34
	3086	176	145.8	155	90	106	62
	3087	185	150.7	295	70	196	46
	3088	180	148.0	205	35	139	24
Arithmetic mean						165 ± 13	38 ± 9
15	3147	160	136.8	195	90	143	66
	3148	182	149.1	575	90	386	60
	3150	180	148.0	280	75	189	51
	3151	180	148.0	550	120	226	81
	3153	176	145.8	425	175	291	120
	3154	185	150.7	215	100	143	66
	3157	158	135.7	410	180	302	133
Arithmetic mean						241 ± 32	82 ± 11

14. Geist, S. H., and Goldberger, M. A.: Am. J. Obst. & Gynec. **12**:206, 1926.

TABLE 1a.—*Breaking Strength and Ratio for Fractured Right and Unfractured Left Fibulae of Ovariectomy Fractured Group—Continued*

Postoperative Days	Rat No.	Weight (W) Operation	Weight (W) $(10.W)^{2/3}$	Force (F) Left	Force (F) Right	Ratio (R) Left	Ratio (R) Right
21	3163	162	137.9	250	215	181	178
	3164	172	143.6	325	200	226	159
	3165	180	148.0	210	85	142	57
	3166	154	133.4	305	140	229	105
	3167	152	132.2	245	215	185	163
Arithmetic mean						193±15	125±20
27	3379	150	131.0	355	225	271	256
	3380	160	136.8	420	295	307	216
	3381	162	137.9	355	225	257	163
	3383	142	126.3	415	275	329	218
	3384	160	136.8	455	250	333	183
Arithmetic mean						299±14	207±15
30	3527	185	150.7	360	125	239	88
	3622	170	142.5	505	210	354	147
	3623	172	143.6	350	275	244	192
	3624	170	142.5	350	275	246	193
	3625	150	131.0	330	230	252	176
	3626	180	148.0	290	95	196	64
Arithmetic mean						255±20	143±21

TABLE 2a.—*Breaking Strength and Ratio for Fractured Right and Unfractured Left Fibulae of Ovariectomy Control Group*

Postoperative Days	Rat No.	Weight (W) Operation	Weight (W) $(10.W)^{2/3}$	Force (F) Left	Force (F) Right	Ratio (R) Left	Ratio (R) Right
9	3786	190	153.4	560	30	365	20
	3787	165	139.7	420	0	301	0
	3788	165	139.7	600	225	429	161
	3789	180	148.0	355	235	240	159
	3790	165	139.7	360	0	258	0
	3678	173	144.1	580	175	403	121
Arithmetic mean						333±29	77±30
15	3668	168	141.4	385	275	272	194
	3670	150	131.0	360	225	275	172
	3671	194	155.6	460	340	296	219
	3672	153	132.8	440	160	331	120
	3669	178	146.9	375	105	255	71
Arithmetic mean						286±12	155±24
21	3684	186	151.3	460	35	304	23
	3685	168	141.4	550	240	389	170
	3686	180	148.0	480	25	324	17
	3687	196	156.6	430	145	275	93
	3683	172	143.6	365	420	254	292
Arithmetic mean						309±21	119±47
27	3688	170	142.5	300	245	211	172
	3689	180	148.0	300	270	203	182
	3690	164	139.1	415	340	298	244
	3692	173	144.1	560	250	389	173
	3691	162	137.9	400	240	290	174
Arithmetic mean						278±31	189±13
30	3673	156	134.6	365	200	271	149
	3675	168	141.4	310	240	219	170
	3674	165	139.7	440	90	315	64
	2322	182	149.1	225	240	151	161
Arithmetic mean						239±31	136±21

TABLE 3a.—*Body Weights and Food Consumed by Rats of Ovariectomy Fractured Group*

| Postopera-tive Days | Rat No. | Weight | | | Food Consumed | |
		Start	Operation	Death	Start to Operation	Operation to Death
9	3051	175	178	180	60	60
	3052	180	170	165	40	40
	3053	170	172	164	61	39
	3056	186	176	180	53	50
	3057	180	185	192	54	60
	3058	175	180	172	61	53
Arithmetic mean............		178	177	176	55	50
15	3147	176	166	168	55	92
	3148	185	182	148	42	67
	3150	175	180	168	58	76
	3151	180	180	174	50	84
	3153	180	176	128	44	37
	3154	185	185	180	53	111
	3157	170	158	180	34	86
Arithmetic mean............		179	175	164	48	70
21	3163	166	162	146	46	111
	3164	170	172	194	78	174
	3165	174	180	178	65	156
	3166	153	154	158	53	168
	3167	152	152	142	46	107
Arithmetic mean............		163	164	164	58	143
27	3379	139	150	102	52	94
	3380	160	160	116	26	101
	3381	162	162	134	35	100
	3383	140	142	110	42	95
	3384	170	160	132	41	114
Arithmetic mean............		156	155	119	39	101
30	3527	176	185	194	42	173
	3622	168	170	165	53	131
	3623	165	172	140	55	120
	3624	178	170	176	70	125
	3625	162	150	140	38	121
	3626	180	180	172	48	213
Arithmetic mean............		172	171	165	51	147

Summary

Postopera-tive Days	Weight at Operation, Gm.	Difference in Weight from Operation to Death, Gm.	Food Consumed per Day from Operation to Death, Gm.	Difference in Weight from Operation to Death as per Cent of Weight at Operation	Food Consumed per Day from Operation to Death as per Cent of Weight at Operation
9	177	— 1	5.6	— 0.6	3.2
15	175	—11	5.8	— 6.3	3.0 ·
21	164	0	6.8	0	4.1
27	155	—36	3.7	—23.2	2.4
30	171	— 6	4.9	— 3.5	2.9

TABLE 4a.—*Body Weights and Food Consumed by Rats of Ovariectomy Control Group*

| Postopera-tive Days | Rat No. | Weight | | | Food Consumed | |
		Start	Operation	Death	Start to Operation	Operation to Death
9	3786	185	190	170	53	30
	3787	152	165	155	60	52
	3788	164	165	160	55	60
	3789	165	180	180	62	65
	3790	155	165	165	48	92
	3678	170	173	187	50	62
Arithmetic mean.......... ..		165	173	170	55	60

TABLE 4a.—*Body Weights and Food Consumed by Rats of Ovariectomy Control Group—Continued*

Postopera-tive Days	Rat No.	Weight			Food Consumed	
		Start	Operation	Death	Start to Operation	Operation to Death
15	3668	158	168	152	57	75
	3670	150	150	140	46	61
	3671	175	194	150	66	89
	3672	158	133	120	46	39
	3669	150	178	140	65	73
Arithmetic mean.	....	158	169	146	56	68
21	3684	168	186	175	62	121
	3685	160	168	160	45	87
	3686	182	180	165	48	85
	3687	180	196	175	62	118
	3683	158	172	140	66	72
Arithmetic mean.............		170	180	165	57	97
27	3688	164	170	142	40	120
	3689	180	180	140	40	133
	3690	165	164	150	54	135
	3692	165	173	145	57	118
	3691	156	162	130	47	115
Arithmetic mean.............		166	170	141	48	122
30	3673	155	156	135	53	157
	3675	170	168	140	54	105
	3674	170	165	140	88	125
	2322	182	182	182	74	182
Arithmetic mean.............		169	168	149	55	142

Summary

Postopera-tive Days	Weight at Operation, Gm.	Difference in Weight from Operation to Death, Gm.	Food Consumed per Day from Operation to Death, Gm.	Difference in Weight from Operation to Death as per Cent of Weight at Operation	Food Consumed per Day from Operation to Death as per Cent of Weight at Operation
9	173	— 3	6.7	— 1.7	3.9
15	169	—23	4.4	—13.6	2.6
21	180	—15	4.6	— 8.3	2.6
27	170	—29	4.5	—17.1	2.6
30	168	—19	4.7	—11.3	2.8

SYPHILIS OF THE STOMACH

WITH SPECIAL REFERENCE TO ITS RECOGNITION AT OPERATION

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Opinions regarding the incidence of syphilis of the stomach are extremely divergent. Judging from the number of cases reported in the past few years by roentgenologists and gastro-enterologists one would conclude that involvement of the stomach is not at all uncommon. For instance, LeWald [1] in 1923 recorded fifty cases examined by himself personally in which the radiologic diagnosis was gastric syphilis. Eusterman [2] in 1930 described observations on ninety-three patients in whom the diagnosis of syphilis of the stomach was made on clinical grounds. Many smaller series are reported by roentgenologists and clinicians both in this country and abroad. The relative frequency of syphilis of the stomach as determined clinically is in sharp contrast to its rarity based on postmortem statistics (see Konjetzny [3]). Pathologists in general are therefore inclined to look on most clinical reports as unreliable. Their attitude is tersely expressed in a statement by Sternberg [4] that merely the number of *reports,* not the number of *cases* of syphilis of the stomach, has increased.

In a previous publication dealing with the incidence of gastric syphilis we [5] upheld the clinician's point of view in contending that the disease was not particularly uncommon. We attempted to explain the

1. LeWald, L. T.: Syphilis of the Stomach; Roentgen Appearance Before and After Treatment, Radiology **1**:193 (Dec.) 1923.

2. Eusterman, G. B.: Gastric Syphilis: Observations Based on Ninety-Three Cases, J. A. M. A. **96**:173 (Jan. 17) 1931.

3. Konjetzny, G. E., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 7, pt. 2, p. 1015.

4. Sternberg, C., quoted by Windholz, F.: Ueber erworbene Syphilis des Magens, Virchows Arch. f. path. Anat. **269**:384, 1928.

5. Singer, H. A., and Meyer, K. A.: Syphilis of the Stomach, with Special Reference to Its Incidence, Surg., Gynec. & Obst. **48**:23 (Jan.) 1929.

rarity with which the disease was seen by the morbid anatomist in the following manner: The suggestion was made and evidence submitted to show that generally at the time a patient with gastric syphilis reaches the autopsy table the lesion either has completely resolved or has lost its specific characteristics in undergoing transformation into scar tissue. According to this assumption, the pathologist encounters the disease usually in an unrecognizable form or in a stage in which the histologic characteristics are not classic. The clinician, on the other hand, is frequently afforded the opportunity of detecting the disease at the height of its activity and of watching its disappearance either spontaneously or following therapy. It is not to be inferred from the foregoing statements that we consider the disease to be a common one, and that we accept the diagnosis of gastric syphilis in most of the reported cases. As a matter of fact, we have been led to conclude that the number of nonsyphilitic cases mistaken for those of syphilis is greater than the number of specific cases overlooked (see Singer and Meyer[6]). The view that we entertain based on a combined clinical and pathologic study is that the disease is neither rare nor common. We believe that any surgeon who performs a considerable number of gastric operations should expect to encounter a syphilitic stomach from time to time but only at relatively long intervals.

The recognition of syphilis of the stomach at the operating table is of great importance, not alone for academic, but also for practical reasons. When the granulomatous infiltrate is sufficiently thick to be readily visible and palpable, the lesion is most commonly mistaken for carcinoma. The latter diagnosis indicates wide resection, a procedure that carries with it a mortality by no means negligible. Syphilitic involvement, on the other hand, generally requires no surgical procedure with regard to the stomach other than removal of tissue for biopsy. When an obstruction is present, gastro-enterostomy suffices. Resection is seldom required. The importance of avoiding extensive operations in gastric syphilis is emphasized by the frequent inability of wounds to heal in the presence of active syphilis. In cases in which the granulomatous infiltrate is relatively thin, the lesion can easily be overlooked, as will be shown later, unless the surgeon is acquainted with the specific anatomic characteristics. The failure to recognize the presence of a lesion of this type causes the surgeon to refrain from performing a gastro-enterostomy that might be indicated (see Larimore,[7] case 3).

6. Singer, H. A., and Meyer, K. A.: Syphilis of the Stomach, with Special Reference to Its Misdiagnosis, Am. J. Surg., to be published.

7. Larimore, J. W.: Syphilis of the Stomach, Surg., Gynec. & Obst. **37**:133 (Aug.). 1923.

It tends also to mislead the gastro-enterologist, who may then assume that the condition is functional and therefore omit anti-syphilitic treatment.

The question naturally arises are the changes in syphilis of the stomach sufficiently distinctive to permit its recognition at laparotomy? We have been impressed, in recollecting our own cases and those reported in the literature or described to us by our colleagues, by the relative ease with which gastric syphilis in general is distinguished from ulcer or carcinoma. It is the exception rather than the rule for a surgeon who has had a fair amount of experience in gastric work to fail to recognize that he is dealing with an atypical type of lesion when he encounters syphilis of the stomach. For instance, LeWald [8] in discussing one of his cases reported from the radiologic standpoint stated, "The surgeon, on inspection and palpation of the growth, immediately said that he was convinced that the lesion was not due to carcinoma or to ulcer of the stomach and did not perform resection." If the operator has dealt with a similar case previously and learned that it was syphilitic, he generally suspects the diagnosis in the second case almost at once. Experience with a few cases is sufficient to permit the surgeon to make the diagnosis with a fair degree of confidence. Even without this experience, a theoretical knowledge of the gross characteristics of syphilis of the stomach generally leads to its identification. A frozen section of tissue taken for biopsy, as will be shown, is of little value in the diagnosis as compared with the gross examination.

Although numerous articles on gastric syphilis have appeared in surgical journals, none, so far as we have been able to ascertain, has dealt at any length with the gross features of the disease. Since at operation the lesion is recognized mainly by its macroscopic characteristics, it is deemed advisable to summarize the morphologic changes that serve to distinguish gastric syphilis from other gastric conditions. In the following paragraphs only those structures that are available for direct examination through an upper abdominal incision will be discussed. The presence of associated lesions elsewhere which are of aid in diagnosis, but which do not lend themselves to inspection at laparotomy, for instance an aneurysm of the thoracic aorta as recorded by Windholz,[9] will receive no special consideration.

It is to be borne in mind that the description which follows applies to the general run of cases, and that variations occur depending on the location, extent and stage of development of the granulomatous involvement. The lesion is most frequently found in the pars pylorica, often

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8. LeWald, L. T.: Roentgen Diagnosis of Gastric Syphilis, J. A. M. A. **96**:*179* (Jan. 17) 1931.

9. Windholz, F.: Ueber erworbene Syphilis des Magens, Virchows Arch. f. path. Anat. **269**:384, 1928.

producing obstruction to the gastric outlet. Less frequently, the process is located in the pars media. Involvement of the pars cardiaca is uncommon. Multiple localizations, especially in the pyloric and mid-portions of the stomach, are not rare. Separate lesions of the cardiac and middle thirds of the stomach as reported by Bensaude, Mezard and Godard [10] are relatively unique. The extent of the lesion varies between wide limits. The granuloma may be restricted to any of the three portions of the stomach mentioned, but also may involve any two or all three. A general involvement of the stomach is rare. Not infrequently, however, the middle and distal thirds of the stomach are simultaneously affected. Early in the disease, the lesion consists of a local, plaquelike infiltrate, which merely imparts a sense of thickening to the palpating hand. A lesion of considerable extent and thickness represents a further stage and is likely to be accompanied by secondary ulceration. Contraction of a segment, usually represented by a concentric, cylindric narrowing, is indicative of a late stage. Diffuse involvement of the stomach is followed by microgastria or leather-bottle stomach. It is to be remembered that up to a certain stage in its development the process is reversible. A thickened, rigid tube encountered at a primary laparotomy may, following specific treatment, as related by Le Noir,[11] be found supple, pliable, normally thin and patent at a subsequent operation.

In considering first the stomach itself, one is struck by the discrepancy in many cases between the radiologic and the anatomic changes. The x-ray picture may suggest the presence of an extensive lesion, whereas at operation one is surprised to see and feel but little anatomic alteration. Schlesinger [12] also mentioned that at laparotomy palpation may fail to disclose an abnormality, although the x-ray picture may reveal considerable deformity. The presence of pyloric stenosis was shown roentgenologically in a case reported by Eisenklam [13] and examined in Holzknecht's institute, which failed to show any anatomic narrowing at operation. A similar case examined by two qualified radiologists was reported by Petit-Dutaillis and Bertrand.[14] In the

10. Bensaude, R.; Mezard, J., and Godard, P.: Sur un cas de syphilis gastrique suivi pendant 20 ans, Arch. d. mal. de l'app. digestif **20**:1178 (Dec.) 1930.

11. LeNoir, P.: Syphilis et ulcére gastro-duodenal, Arch. d. mal. de l'app. digestif **20**:470 (April) 1930.

12. Schlesinger, H.: Die Magensyphilis, Klin. Wchnschr. **9**:171 (Jan. 25) 1930.

13. Eisenklam, I.: Ueber diffuse luetische Infiltration des Magens, Wien. klin. Wchnschr. **39**:182 (Feb. 11) 1926.

14. Petit-Dutaillis, D., and Bertrand, I.: Un cas curieux de syphilis gastrique grave sans tumeur, simulant le cancer. Vérification biopique. Gastro-entérostomie combinée au traitement spécifique. Guérison, Arch. d. mal. de l'app. digestif **20**: 199 (Feb.) 1930.

paucity of anatomic as compared with radiologic changes, gastric syphilis is in contrast to carcinoma, in which unfortunately the lesion is generally much more extensive than anticipated from its appearance in the x-ray picture.

The characteristic lesion of syphilis is a flat, plaquelike infiltrate that involves the submucosa principally. The most distinctive feature of this infiltrate is its relatively soft consistency. When the infiltrate is thin, it may be entirely overlooked, because it fails to impart the expected increased sense of resistance detected in carcinoma or ulcer. The softness combined with the flatness of the infiltrate readily leads to an oversight. Windholz [9] described a pertinent case of a woman of 36 who was subjected to an operation for what was interpreted roentgenologically as a new growth of the cardiac portion of the stomach. At operation no gastric lesion was detected, and the abdominal incision was closed. Later examination with a barium meal showed an extension of the process, and a second operation was undertaken. This time tissue for biopsy was removed, and histologic changes suggestive of syphilis were found. Gradual decrease in the size of the stomach in spite of antisyphilitic treatment later necessitated a gastrostomy. The patient died about one year after the original operation with typical subtotal linitis plastica of syphilitic nature. The radiologic aspects of the case were described by Schwarz [15] in a separate communication. Petit-Dutaillis and Bertrand [14] related that in a patient in whom gastric syphilis was encountered at operation they were unable to detect any noteworthy change in the wall of the stomach before incising it. Palpation gave at most the impression that the pylorus was a little thickened and indurated. The x-ray picture showed what was interpreted as linitis plastica of the pyloric portion of the stomach. The tissue for biopsy removed from the region chosen for a gastro-enterostomy stoma showed microscopically that the infiltration had extended far beyond the pars pylorica. A similar case (no. 3) was reported from the roentgen standpoint by Larimore.[7] The x-ray picture showed an annular defect of the pyloric portion of the stomach producing high grade obstruction. At the operation, no gastric lesion was identified by the surgeon. In the first of the two cases to be described in this paper, only a portion of the infiltrate beyond the pylorus was detected by the surgeon at the operating table.

When the infiltrate leads to noteworthy thickening of the wall of the stomach, the presence of a lesion is, of course, readily recognized. Its relatively soft consistency and its plaquelike form, however, serve to distinguish it from carcinoma and from the inflammatory tumor that

15. Schwarz, G.: Die Entwicklung eines syphilitischen Schrumpfmagens im Röntgenbilde beobachtet, Fortschr. a. d. Geb. d. Röntgenstrahlen 37:313, 1928.

frequently accompanies ulcer. Except in leather-bottle types with marked shrinkage, the gastric wall is pliable and is only moderately increased in consistency as compared with the normal. The consistency of the infiltrate is fairly uniform, except at its margins, where it merges almost imperceptibly into the surrounding normal gastric wall. The degree of thickening varies between wide limits. However, irrespective of the amount of thickening, the point of maximum increase is in the center of the lesion, and the transition from the normal to the abnormal is a very gradual one. The great majority of lesions reported in the literature as well as in our own series answer to the foregoing description.

In addition to the characteristics described as determined by palpation, there are a few features noted on inspection which, although less distinctive, merit description. The peritoneum over the involved area is thickened, lusterless, opaque and often edematous. Aoyama [16] stated that he suspected the fourth case in his series of being syphilitic by the appearance of the exterior of the stomach. He noted more or less widespread whitish thickening, edematous swelling and focal injection. Occasionally, the surface of the stomach is reddened as in the case reported by Eisenklam.[13] However, this is not typical and is apparently due to secondary infection. Adhesions are generally absent, but may be prominent as in the second case to be described later.

Incision into the stomach often yields valuable information. If the wall is incised in the area of infiltration, i. e., for the purposes of a biopsy, the cross-section of the stomach will show the individual coats to be distinct. Extensions from the mucosa into the subjacent layers as in carcinoma are lacking. The thickening of the wall of the stomach is seen to be due to an increase chiefly of the submucosa, which is rendered homogeneous and edematous. The tissue here has fibrous rather than neoplastic characteristics. Exposure of the interior surface of the lesion by an opening made beyond the margin of infiltration often discloses more or less ulceration. The ulcers are frequently multiple and are irregular in shape with serpiginous outlines. The edges are only slightly raised and are not undermined. The floor of an ulcer is generally covered by a lardaceous membrane, which is lightly adherent. The ulcers are superficial, the floor being generally formed by the underlying thickened submucosa. The base of the ulcer is generally in the same niveau as the margins and projects above the level of the normal mucosa. The ulceration occupies the thickest portion of the granuloma, and thereby furnishes the impression that the denudation is secondary to the infiltration. Although superficial, the ulcers tend to

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16. Aoyama, T.: Ueber syphilitische Erkrankung des Magens, Deutsche Ztschr. f. Chir. **174**:34, 1922.

be large, often reaching the size of the palm of a hand or larger (see fig. 2). Occasionally one finds extensive ulceration within which one or more islands of remaining mucosa are found (McNee,[17] Singer and Meyer[5] [case 2], Sparman[18]).

Of great assistance in the diagnosis at laparotomy are certain associated changes of syphilitic nature occurring particularly in the liver and the small intestine. The most frequent syphilitic lesion encountered in the abdomen is hepatic. The high incidence of syphilis of the liver in association with cases of gastric syphilis has been emphasized by Schlesinger.[15] Multiple deep stellate scars producing a classic hepar lobatum as occurred in the cases of Derman and Kopelowitsch[19] and Petit-Dutaillis and Bertrand[14] should immediately arouse the suspicion of syphilis when a gastric lesion co-exists. Less typical changes, such as limited scarring involving especially the left lobe and the region of the suspensory ligament as recorded by Windholz,[9] in his case 2, are also suggestive. Cicatrices limited to the right lobe, especially when superficial as in case 1 reported here, are of less significance. Practically complete shrinkage of the left lobe and involvement in the region of the attachment of the round ligament, with compensatory hypertrophy of the right lobe, are almost pathognomonic of syphilis of the liver. This type of lesion was found in Brams'[20] classic case of gastric syphilis. A similar hepatic involvement was encountered by Kwartin and Heyd[21] in their third case. Actual gummas, as might be expected, are less frequently encountered than scars. The presence of nodules in the liver may suggest carcinoma. The coexistence of gummas and scars as in one of our previous cases (Singer and Meyer[5]) should serve to identify the syphilitic nature of the nodules. A specimen for biopsy taken from one of the hepatic tumors as in case 4 of Downes and LeWald[22] would likewise aid in the diagnosis. The coincidence of syphilis of the liver and carcinoma of the stomach as mentioned by Gatewood and Kolodny[23] is constantly to be borne in mind by the

17. McNee, J. W.: Syphilis of the Stomach, Quart. J. Med. **15**:215, 1921-1922.

18. Sparman, R.: Ein Fall von Magen-Dünndarmsyphilis, zugleich ein Beitrag zur Kenntnis syphilitischer Magen-Darmerkrankungen, mit besonderer Berücksichtigung gummöser Veränderungen am Magen, Deutsche Ztschr. f. Chir. **164**: 136, 1921.

19. Derman, G. L., and Kopelowitsch, M. A.: Zur pathologischen Anatomie der syphilitischen Magengeschwüre, Virchows Arch. f. path. Anat. **278**:149, 1930.

20. Brams, W. A.: Ueber das Ulcus syphiliticum multiforme ventriculi, Arch. f. Verdauungskr. **27**:375, 1921.

21. Kwartin, B., and Heyd, C. G.: Syphilitic Ulcerations of the Stomach, Arch. Surg. **14**:566 (Feb.) 1927.

22. Downes, W. A., and LeWald, L. T.: Syphilis of the Stomach: A Report of Eight Cases with Roentgenologic Findings, J. A. M. A. **64**:1824 (May 29) 1915.

23. Gatewood, W. E., and Kolodny, A.: Gastric and Intestinal Syphilis: Report of a Case; Clinical Course and Morbid Pathology, Am. J. Syph. **7**:649 (Oct.) 1923.

surgeon. Syphilitic lesions involving the small intestine and the spleen are less common and less easily identified. The lesions of the small intestine tend to be multiple. Fraenkel's [24] case is a prototype of the gastro-intestinal form. Splenomegaly, according to Schlesinger,[25] is present only exceptionally. However, its detection should lead to a search for a cause.

Syphilitic lesions of the stomach often require laparotomy. The obstructive lesions of irreversible character and acute perforation obviously demand surgical intervention. However, aside from the vital indications, operation is frequently essential for identification of the lesion. The diagnosis of gastric syphilis is difficult in many cases principally on account of the close resemblance it bears to carcinoma. A filling defect in the stomach even in the presence of a positive Wassermann reaction, on the basis of statistics, is more likely to represent a malignant than a syphilitic process (Singer and Meyer [6]). The frequency of gastric carcinoma and the high incidence of constitutional syphilis render the diagnosis of gastric syphilis a hazardous one. On this account, Baumecker [26] considered laparotomy imperative. Although the therapeutic test can be invoked to aid in the determination of the nature of the lesion, there are certain limitations and disadvantages to this procedure. Although opinions differ somewhat regarding the length of time of trial, it is generally agreed that only a relatively short period is warranted. Stokes [27] advised in questionable cases the preoperative administration of two injections of arsphenamine, 0.3 Gm. each, with a three day interval. If improvement within seven days is not pronounced, and if the operability of the patient may be decreased by further delay, an exploration should be performed. Sinakevitch and Toporkoff [28] suggested treatment for from ten to fifteen days. Einhorn [29] recommended a test period of from two to four weeks or longer. Bockus and Bank [30] stated that Eusterman believed that six weeks is adequate to test the effect of antisyphilitic treatment.

24. Fraenkel, E.: Zur Lehre von der acquirirten Magen-Darmsyphilis, Virchows Arch. f. path. Anat. **155**:507, 1899.

25. Schlesinger, H.: Syphilis und innere Medizin, Vienna, Julius Springer, 1926, pt. 2, p. 121.

26. Baumecker, H.: Die klinische Diagnose der hypertrophischen Magenlues, Med. Klin. **26**:1557 (Oct. 17) 1930.

27. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1927, p. 734.

28. Sinakevitch, N. A., and Toporkoff, N. N.: Syphilis of the Stomach from the Viewpoint of Surgery and Neuropathology, Vestnik khir. **21**:3, 1930.

29. Einhorn, M.: Syphilom des Magens. Heilung durch antiluetische Kur, Deutsche med. Wchnschr. **55**:1877 (Nov. 8) 1929.

30. Bockus, H L., and Bank, J.: Upper Gastrointestinal Disease Associated with Syphilis, Am. J. Syph. **13**:30, 1929.

The value of the therapeutic test is limited, whether it is applied for one or for six weeks, since a fair proportion of syphilitic patients fail to show appreciable improvement. For example, in case 2 of LeWald,[8] after five weeks of treatment the degree of improvement was so slight that resort to exploratory operation was deemed advisable. The lesion at operation was shown to be syphilitic. In case 7 of the series published by Bockus and Bank,[30] six months of intensive treatment was necessary before improvement became noticeable. We among others have had similar experiences. Another disadvantage of the therapeutic test is that at times it is misleading. For example, a patient with gastric carcinoma and constitutional syphilis may improve temporarily as a result of antisyphilitic treatment. This observation is attested to by O'Leary.[31] Stokes [27] mentioned a case of carcinoma in which sufficiently marked improvement was obtained to lead to the temporary diagnosis of syphilis, which was later reversed by the disclosure at operation when the patient finally began to decline again. We have had similar experiences (Singer and Meyer [6]). The most serious objection to the therapeutic test, however, is the time lost in the event that the lesion proves to be carcinomatous. The local extension of the neoplasm may not be as significant as its constitutional effect, which decreases the patient's vitality and renders him a poorer surgical risk. The seriousness of overlooking a carcinoma and the relative innocuousness of a laparotomy in the presence of gastric syphilis have led not only surgeons but also internists and syphilologists (see Gäbert,[32] Schlesinger,[12] Stokes [27] and Strauss [33]) to recommend surgical intervention, unless otherwise contraindicated, whenever the slightest suspicion of carcinoma is entertained.

In the recognition of gastric syphilis the surgeon cannot depend on the standpoint of positive diagnosis. Unlike carcinoma or sarcoma unlike one in carcinoma, for instance, is of limited value, at least from the standpoint of positive diagnosis. Unlike carcinoma or sarcoma, gastric syphilis presents no pathognomonic histologic changes. As pointed out in a previous publication (Singer and Dyas [34]), the specific lesion of syphilis, i. e., the gumma, as found, for instance, in the liver, has not been described in the stomach. The histologic diagnosis is based on the recognition of several characteristics occurring in combination rather than on any one specific feature. The demonstration of these

31. O'Leary, P. A.: Gastric Syphilis: Data Accumulated from 89 Cases, Am. J. Surg. **11**:286 (Feb.) 1931.

32. Gäbert, E.: Zur Kenntnis und Diagnose der Magensyphilis, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **40**:224, 1927-1928.

33. Strauss, H.: Ueber Magen-Syphilis, Med. Klin. **27**:275 (Feb. 20) 1931.

34. Singer, H. A., and Dyas, F. G.: Syphilis of the Stomach, with Special Reference to Certain Diagnostic Criteria, Arch. Int. Med. **42**:718 (Nov.) 1928.

characteristics usually requires sections from several areas and also special stains. A single section rapidly prepared and stained with hematoxylin and eosin or polychrome stains during the course of an operation generally fails to yield information that will permit even a presumptive diagnosis of syphilis. In actual practice, tissue for biopsy is generally removed from the margin of the lesion because of the difficulty in suturing the defect if the center of the lesion is chosen. Generally, the histologic changes at the periphery of the syphilitic infiltrate are at the most only suggestive of a specific infection. This statement is borne out by the experience of Windholz,[9] in whose second case the tissue for biopsy removed at operation failed to show the typical changes that were later demonstrated in the central portions of the lesion at autopsy. The greatest value of a biopsy in syphilis of the stomach lies in its negative worth, i. e., in excluding carcinoma, provided, of course, the section chosen is representative of the lesion present.

Even if biopsy material is obtained from several areas and the preparations are stained by various methods, the information derived from the microscopic study alone is often insufficient on which to base a diagnosis. Some of the most expert histopathologists (Fraenkel,[24] Erdheim [Sparman's [18] case]) require the presence of certain gross features before concluding that a lesion is syphilitic, even though the microscopic changes are typical. In the cases of Mühlmann,[35] and Gosset et al.,[36] the histologic examination proved of limited worth in the identification of the lesion, as compared with the gross appearance. Eusterman [2] in speaking of the patients in his series who were operated on, stated, "Resected specimens were obtained in 14 clinically authentic or probable cases. Biopsy specimens, several of them unsatisfactory, were obtained in five others." The inference to be drawn is that the biopsies failed to show microscopic changes that were as distinctive of syphilis as the clinical and gross anatomic characteristics. Our own observation has been that the more experience one acquires with syphilis of the stomach the more weight does one place on the macroscopic features in arriving at a diagnosis. In the last three cases that came under our observation we were able to make the diagnosis with confidence from the gross character of the lesion. The tissue taken for biopsy in each instance was reported by a competent pathologist as showing chronic, nonspecific inflammation. In the second case recorded here, the diagnosis of syphilis is not justified by the histologic appearance of the

35. Mühlmann, E.: Beiträge zum Schrumpfmagen auf luetischer Basis, Deutsche med. Wchnshr. **41**:733 (June 17) 1915.

36. Gosset, A.; Guttman, R. A., and Bertrand, I.: Syphilis gastrique infiltrée à forme tumorale. Résection. Examen histologique, Arch. d. mal. de l'app. digestif **20**:714 (June) 1930.

tissue taken for biopsy, yet the other available data, viz., the presence of syphilis, the therapeutic response, the subsequent course and especially the macroscopic nature, establish the diagnosis almost beyond any question of doubt.

We disagree with Kwartin and Heyd,[21] who contended that final judgment should rest on the microscopic changes, and that the macroscopic picture cannot be accepted as sufficiently clearcut to permit even a preliminary diagnosis. These authors report three cases all with macroscopic features generally considered characteristic of syphilis. In the first case, the histologic examination confirmed the gross diagnosis. In the second case, however, the microscopic diagnosis of tuberculosis was favored, and in the third a nonspecific etiology was assumed. Without attempting to enter into polemics, we wish to point out our reasons for believing that these authors have fallen into error by placing most emphasis on the histologic picture. In their case 2, the lesions described as histologically characteristic of tuberculosis are not at all unlike miliary gummas seen in syphilis of the stomach and other structures. Practically identical lesions were described by Fraenkel[24] in the lymph nodes, as well as in the gastro-intestinal tract, in his case of gastric syphilis, in which the diagnosis was almost unequivocally established. The "periarterial, endarterial and panphlebitic changes" such as were recorded by Kwartin and Heyd[21] in this second case are more likely to be syphilitic than tuberculous in origin. The absence of tubercle bacilli in histologic preparations likewise throws doubt on their diagnosis of tuberculosis of the stomach. In case 3 of Kwartin and Heyd again, we are inclined to look on the gross diagnosis as correct, although the microscopic appearance is not characteristic of syphilis. Hepatic involvement near the round ligament and absence of the left lobe of the liver, which were found in their third case, are pathognomonic of hepatic syphilis. The history of a positive Wassermann reaction in the husband's blood is also confirmatory evidence, especially since the blood of the patient was not tested. The lack of histologic changes typical of syphilis should not in this case be the decisive factor in arriving at a diagnosis. As has been shown in a previous publication (Singer[37]), in certain stages of the disease the lesions are likely to lose their specific microscopic characteristics in the stomach as they do, for instance, in the liver and rectum. It should be stated that Kwartin and Heyd are aware of many of these considerations and readily admit the difficulties in connection with the microscopic diagnosis of syphilis.

The two cases to be described now are particularly instructive from the standpoint of recognition of gastric syphilis at the operating table.

37. Singer, H. A.: Syphilis of the Stomach, with Special Reference to Its Relationship to Linitis Plastica, Am. J. Syph. **13**:391 (July) 1929.

REPORT OF CASES

CASE 1.—R. M., a colored woman, aged 36, was sent to the Cook County Hospital on July 22, 1931, from one of the local dispensaries with the diagnosis of pulmonary tuberculosis. The basis of the diagnosis made by the dispensary physician was apparently the extreme degree of emaciation, for the patient offered neither subjective nor objective evidence of intrathoracic abnormality. It was soon apparent to the house physician in the tuberculosis division that the cause of the patient's emaciation was an abdominal condition. On this account, roentgen exam-
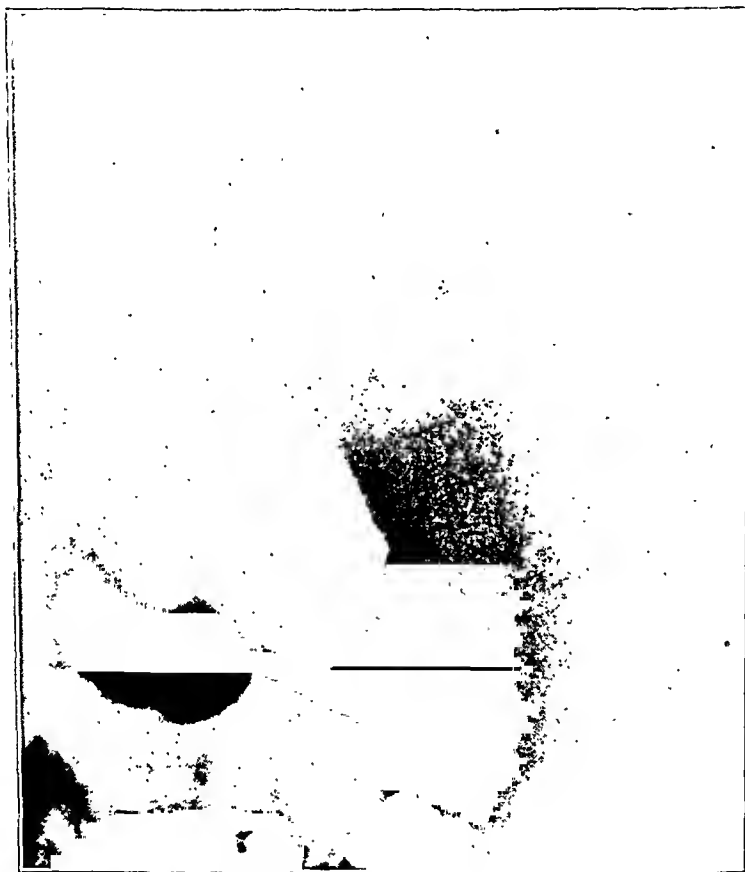
Fig. 1 (case 1).—Roentgenogram showing a spigot-shaped deformity of the prepyloric portion of the stomach due to syphilis.

ination (fig. 1) with a barium meal was requested and the report made on July 23, 1931, was: "Annular constricting deformity of the pyloric portion of the stomach indicative of 'malignancy." The patient was thereupon transferred to the medical service with the diagnosis of pyloric obstruction.

In the medical ward, it was ascertained that the patient began to experience epigastric pain three years prior to admission. Vomiting and loss of weight accompanied the pain. Because of these symptoms she was operated on elsewhere, but was not clear regarding either the nature of the lesion found or the procedure instituted. Following the laparotomy, the vomiting subsided, but only for a short period. The other symptoms were uninfluenced. The pain, which involved the

epigastrium rather diffusely, was described as cramplike and persisted more or less constantly. Neither soda nor emesis afforded relief. During the three years of her illness, the patient had lost 122 pounds (55.3 Kg.), her present weight being 88 pounds (39.9 Kg.). No hematemesis had been noted. Physically, the essential changes included evidence of moderate anemia, extreme emaciation and debility. The pulse was rapid (120) and weak. The blood pressure was 90 systolic and 60 diastolic. Abdominal examination disclosed, in addition to the healed midline scar of the laparotomy, the outline of the stomach projecting above the level of the remainder of the abdomen. No visible peristalsis was observed, and no mass was palpated. On the dorsa of both hands were evidences of dermatitis. The diagnosis of pyloric carcinoma with symptomatic pellagra was made, and the condition of the patient considered terminal. The extreme dehydration and debility, it was thought, precluded the possibility of successful intervention at that time. Fluids were administered by intravenous and subcutaneous routes, following which the giving of liquids by mouth was attempted. Although some vomiting occurred, a fair proportion of the ingested material was retained. No diagnosis other than that of carcinoma was entertained until Sept. 7, 1931, when hematemesis associated with a series of tarry stools appeared. The possibility of a benign gastric ulcer loomed into prominence, and a more optimistic attitude was assumed. The patient was prepared for surgical intervention and operated on on Sept. 9, 1931, at 8 a. m.

The surgeon who performed the operation found the stomach to be somewhat decreased in size. There were adhesions that bound the stomach posteriorly and were particularly marked along the lesser curvature. The serosa was edematous and opaque. The pyloric portion of the stomach was thickened and tubular, but only slightly increased in consistency. The thickening was not limited to the tubular pyloric portion, but extended in the form of a plaque to involve the pars media, which was also relatively soft. The patient's condition was considered too poor to withstand a gastro-enterostomy. However, the surgeon removed a block of tissue from the wall of the stomach for biopsy and closed the laparotomy wound. The patient was returned from the operating room with an extremely rapid and thready pulse. The operating surgeon believed he was dealing with a sarcoma of the stomach, and at the conclusion of the laparotomy sought our opinions. From the surgeon's description of the character of the gastric lesion we immediately suggested the diagnosis of syphilis. No time was lost in examining the x-ray plates, which we felt lent support to our impression. We then attempted to interview the patient, who, although conscious, was too weak to furnish complete and trustworthy information regarding her past. We did learn, however, that she had married at the age of 14 and had had one miscarriage and no children. She denied knowledge of venereal disease. As a Wassermann test had not been performed, we ordered blood drawn for this purpose. The patient became progressively weaker and died at 6:50 p. m., ten hours following operation. The next morning an autopsy was performed, and later in the day the result of the Wassermann test on the blood was reported four plus, and that of the Kahn test two plus.

Anatomic Diagnosis.—The postmortem examination was made twenty hours after death by Dr. R. H. Jaffé, whose anatomic diagnosis reads: "Ulcerative syphilitic gastritis; adhesions and stellate scars of the right lobe of the liver; aspiration pneumonia and abscess in the right upper pulmonary lobe; aspiration pneumonia in the left upper lobe; acinous tuberculosis of the right upper pulmonary lobe; brown atrophy and anemia of the liver; brown atrophy of the heart

and serous atrophy of the subepicardial fat; anemia of the kidneys; adhesions of the base of the right pulmonary lobe; adhesions of both tubes and ovaries; cholesteatosis of the gallbladder; marked emaciation; recent and ancient laparotomy wounds; pellagra-like changes of the skin of the hands."

Gross Appearance of Stomach (Fig. 2).—The unopened stomach was filled with preserving fluid for museum purposes and its interior examined after fixation by removal of a portion of the anterior wall.

The stomach had an anomalous form, the proximal two thirds being globular, the distal one third cylindric. The globular portion consisted of the moderately

Fig. 2 (case 1).—A syphilitic stomach in which the greater portion of the anterior wall has been removed. The granulomatous infiltrate has encircled the pars pylorica (*P*) and transformed it into a narrow tube. The plaquelike thickening of the gastric wall extends along the lesser curvature almost to the cardia (*C*). An extensive, superficial ulcer of serpiginous outline occupies a considerable portion of the surface of the plateau formed by the granulomatous plaque. The esophagus (*E*) is moderately dilated.

dilated pars cardiaca and pars media. The cylindric portion represented a thickened, contracted pars pylorica, which projected like a spout from the remainder of the stomach. The lesser curvature was contracted, measuring 10 cm. The

greater curvature was 35 cm. long. The serosa over the distal portion of the stomach was thickened, white and edematous; in one area on the lesser curvature side, it was rendered quite opaque. The thickening of the serosa extended to involve the covering of the beginning duodenum distally and especially the lesser curvature and posterior wall proximally. On palpation, the distal 4 cm. of the stomach was firm, elastic and thick. Passing toward the cardia along the lesser curvature, the sense of thickness and resistance imparted by the pyloric portion gradually diminished as the esophageal end was reached. The same palpatory observations were made with regard to a plaquelike area involving the anterior and posterior surfaces for a distance of 5 cm. from the lesser curvature. The margins of this thickened plaque passed almost imperceptibly into the surrounding gastric wall.

When the stomach was opened, the pyloric portion was found to be transformed into a more or less concentric tube with a very narrow opening, roughly of funnel shape. The point of maximum constriction was just at the pyloric ring, where the lumen barely admitted a narrow probe. The lining of the tubular portion was rough and mottled gray-red, was firmly attached to the underlying layers and presented areas of wrinkling and puckering. The intact mucosa merged proximally with an extensive shallow ulcer, which corresponded to the area of plaquelike thickening observed on palpation. The ulcer was quite superficial, the outline somewhat serpiginous, the margins in places barely thickened, and the floor covered by a gray, loosely adherent, lardaceous material. In no place did the base of the ulcer extend below the level of the intact mucosa.

Cross-section of the wall of the stomach showed the thickening of the tubular pyloric portion to be due mainly to an increase of both the submucosa and the muscularis. The maximum thickness of the muscular coat was 5 mm., that of the submucous layer 7 mm. The thickness of each layer diminished very gradually in passing proximally until the cardiac end of the ulcer was reached. The submucosa, on section, was white and homogeneous and appeared fibrous.

Septums of whitish fibrous tissue were found in places extending into the muscularis, which in other respects presented a normal appearance. In the involved areas, the mucosa was decreased and the serosa increased in thickness. The portion of stomach free from infiltrate showed, on cross-section, a slightly thickened muscular coat and a thinned mucosa. The submucosa was grossly normal. The attached portion of esophagus was dilated to measure 6 cm. in circumference. Its musculature was likewise hypertrophied. The perigastric lymph glands were generally enlarged, but none exceeded 1.2 cm. in diameter. The glands were semielastic, gray-pink and moist, and on cross-section presented a relatively normal appearance.

Microscopic Observations.—For the sake of brevity merely the outstanding changes will be included. Detailed descriptions of practically identical lesions can be found in previous reports of other cases that we have studied. The mucosa proximal to the large ulcer was thin and contained atrophic glandular elements, which were relatively widely separated. The tunica propria was infiltrated mainly by lymphocytes. Plasma cells and leukocytes were present in small numbers. In one area, the cylindric was replaced by squamous epithelium composed of from 9 to 14 layers of flat cells, which rested on a dense connective tissue base (leukoplakia). In the ulcerated portion, the mucosa was completely destroyed or substituted by a layer of fibrillar connective tissue, which merged with the submucosa. The muscularis mucosae in the ulcerated area was incomplete, being replaced in

part by fibrous elements. Where still preserved, the muscle fibers presented a hypertrophic appearance and were separated by connective tissue.

The submucosa constituted the base of the ulcer over all but a limited portion of its extent. The floor of the ulcer was covered by a thin layer of fibrinoid necrosis and degenerated leukocytes. The submucous coat began to increase in thickness just proximal to the margin of ulceration. As the center of the defect was approached, the maximum thickness of the submucosa was attained. Here it occupied three fifths or more of the gastric wall. This increase was due to young
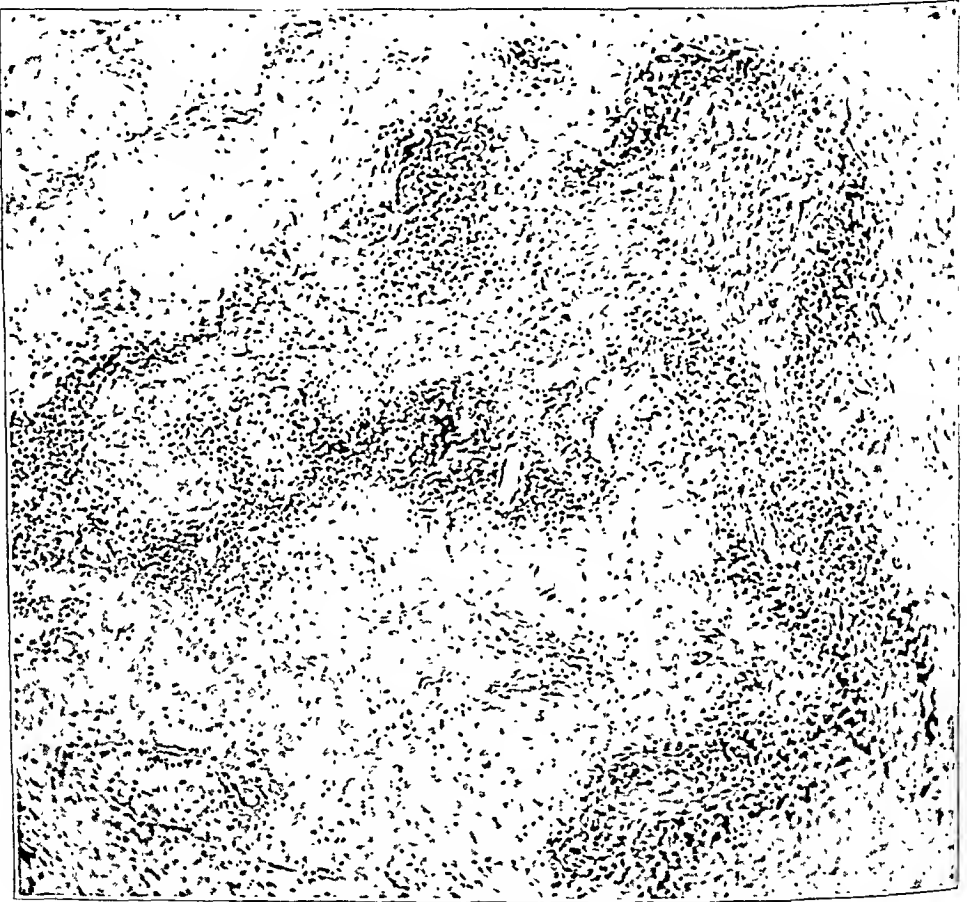
Fig. 3 (case 1).—A photomicrograph of an area in the submucosa illustrating particularly the panvasculitis (hematoxylin and eosin preparation). By special stains (elastica and van Gieson) the infiltrating cells are found to be within and surrounding the walls of blood vessels (see fig. 4). An endarteritis has led to sufficient intimal proliferation to obliterate the vascular channels.

granulation tissue rich in fibroblasts, infiltrated by scattered and grouped lymphoid cells. The blood vessels in this layer showed evidence of severe damage. Indeed, it was only by means of special stains (elastica and van Gieson) that the presence of some of the preexistent vessels could be demonstrated. The panvasculitis is so well exhibited in the accompanying photomicrographs (figs. 3 and 4) that a detailed description would prove superfluous. It may be necessary to add that the infil-

trating cells were mainly lymphoid in type. Plasma cells and macrophages were relatively sparse. The veins were involved to a greater extent than the arteries.

The muscularis propria presented slight thickening of its fibrous septums, within which were found small numbers of lymphoid cells. The serosa was increased to several times its normal thickness owing to proliferated fibrous elements and many leukocytes and lymphoid cells. The only other pertinent microscopic changes were noted in the perigastric lymph nodes and the liver. In the former, the follicles of the cortex were small, and their centers were formed chiefly by swollen and proliferated reticulum cells. The medulla contained numerous plasma cells. Sec-
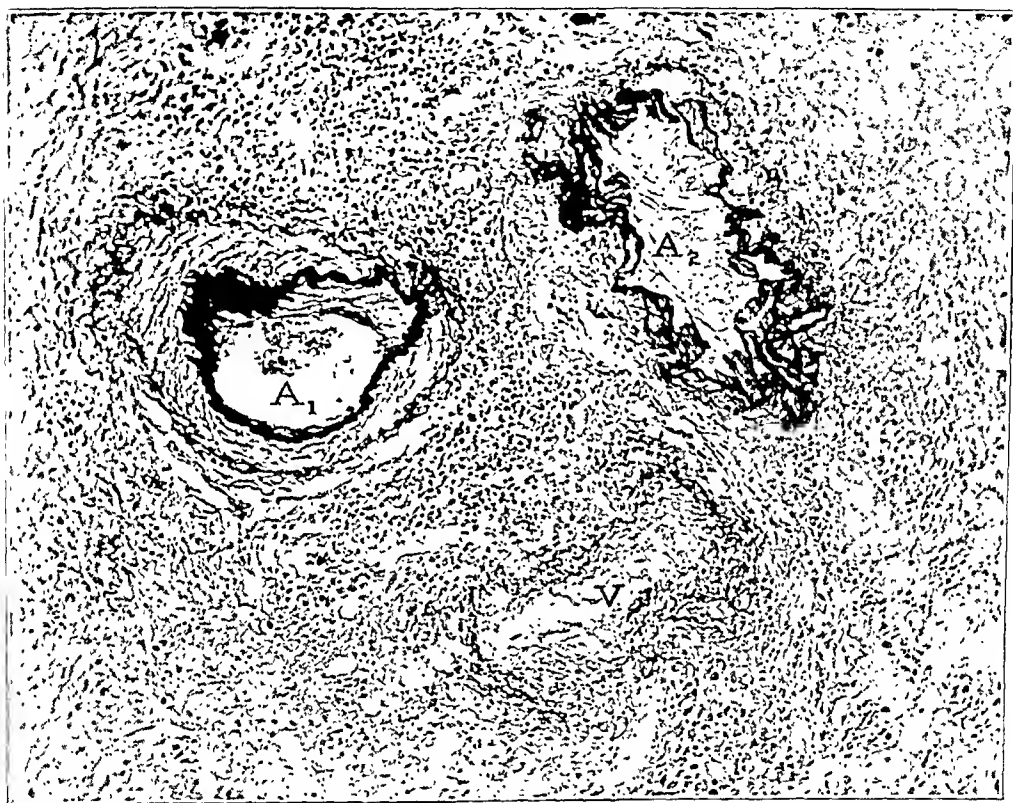
Fig. 4 (case 1).—An elastica preparation from the same block as that shown in figure 3 but somewhat deeper. The elastic fibers of the vein (V) are split and frayed to form a complex network. The internal elastic membranes of the arteries (A_1, A_2) are greatly thickened.

tions from a depressed area in the right hepatic lobe showed a thick strand of dense connective tissue which branched and extended into the hepatic parenchyma. The fibrous strands contained small, thick-walled arteries, bile ducts and scattered and grouped lymphoid cells.

Levaditi preparations contained a moderate number of argentaffine bacilli but no spirochetes bearing a morphologic resemblance to Spirochaeta pallida. Ziehl-Neelsen stains failed to demonstrate any acid-fast organisms. Animal inoculations were not employed.

CASE 2.—J. T., a colored man, aged 28, was admitted to the medical service of the Cook County Hospital on June 11, 1930. On entrance to the hospital his condition was diagnosed as peptic ulcer. He asserted that the very first indication of a gastric disturbance occurred in December of 1929 about six months prior to his hospitalization. He then began to notice epigastric distress occurring from fifteen to thirty minutes after meals and continuing for approximately an hour. The pain was sharp during the first fifteen minutes and gradually subsided following that time. Soda afforded only incomplete relief. Bland foods were better tolerated than coarse or irritating foods.
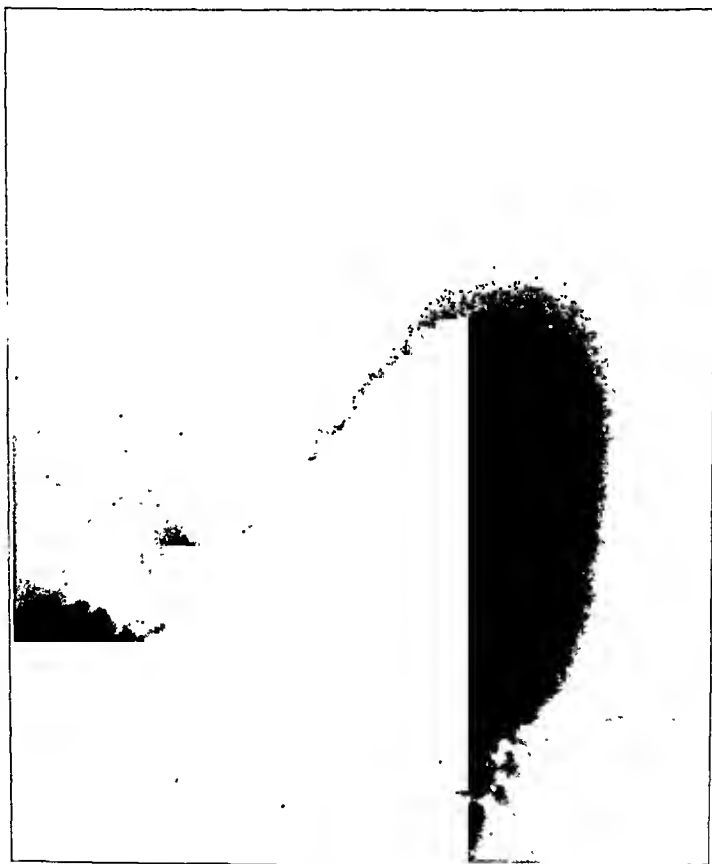
Fig. 5 (case 2).—An irregular, annular constriction of the prepyloric region produced by gastric syphilis prior to treatment.

Vomiting first made its appearance on April 10, 1930, about four months after the onset of the epigastric pain. Emesis was repeated several times during that day and the following day also. Constant pain was present throughout the period of vomiting. The patient consulted a physician, who prescribed Sippy management for ulcer. The patient felt greatly improved, although he continued to vomit at intervals until after the second week of treatment when he was entirely relieved. After three weeks he returned to an unrestricted diet, following which his pain reappeared. On June 7, 1930, four days prior to entrance, persistent vomiting recurred, on account of which the patient sought admission to the hospital.

A general inventory of symptoms by systems yielded no significant information. The patient admitted a gonorrheal infection a year previous, but stated that he had

no knowledge of a chancre. The results of physical examination were essentially negative, except for moderate tenderness in the epigastric region. The first Ewald meal, recovered after forty-five minutes, yielded 300 cc. of poorly digested material with a free acidity of 30 degrees and a total acidity of 70 degrees. A motor meal aspirated six and one-half hours after ingestion contained recognizable food elements in the form of spinach and raisins. A series of stools were weakly but persistently positive for blood. The Wassermann reaction of the blood was reported
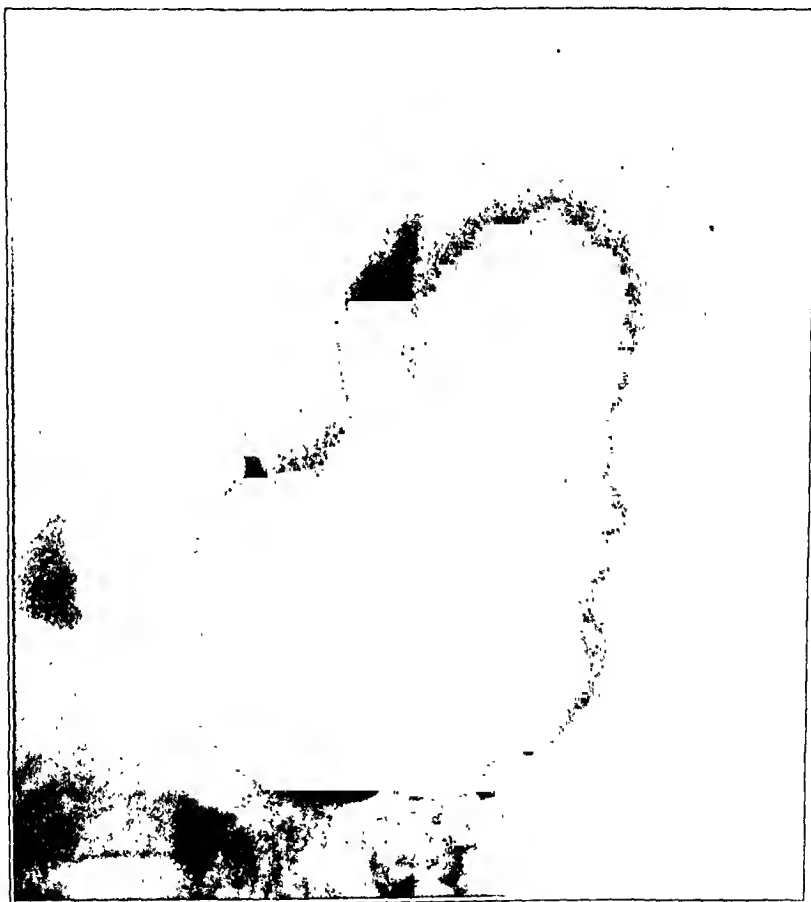
Fig. 6 (case 2).—X-ray film taken two and one-half months after that shown in figure 5, following gastro-enterostomy and a course of antisyphilitic treatment. The degree of narrowing of the prepyloric segment has increased and the deformity has assumed a bizarre outline.

four plus; the Kahn, two plus. The filtered gastric contents gave negative complement fixation, with the use of 0.5 cc. of the fluid. A barium meal revealed (fig. 5) a constant deformity of the pyloric portion of the stomach with obstruction, which were interpreted by the roentgenologist, Dr. C. H. Warfield, as being due to either syphilis or carcinoma.

The patient continued to vomit irregularly on a regimen for patients with ulcer, which included a bland diet. Without attempting antisyphilitic treatment, his

attending physician recommended exploration. The patient was transferred to the surgical service on June 27, 1930, with the diagnosis of gastric syphilis or carcinoma. On the following day, laparotomy was performed by one of us (K. A. M.). The stomach, which was somewhat enlarged, was found to be free from adhesions. Inspection showed the serosa of the prepyloric portion of the stomach to be thickened, whitish and edematous. No tumor mass was visible. Palpation indicated increased thickening of the prepyloric region, but the wall remained fairly pliable. The consistency of the involved area was doughy to semielastic rather than firm as in a scirrhus. The thickening extended to and encroached on

Fig. 7 (case 2).—Histologic appearance of the biopsy specimen removed from the stomach at operation. Except for the upper margin, which consists of gastric tubules and muscularis mucosae, the section is comprised of thickened submucosa. The increase of the submucous layer is due to connective tissue proliferation and cellular infiltration. A perivascular arrangement of the round cells is noted in connection with a venule (*V*).

the pyloric sphincter, causing narrowing of the orifice. No actual tumor mass was palpable. Incision in the longitudinal axis of the stomach into the involved area at its proximal margin showed that the thickening of the wall was due mainly to an increase in the submucous layer, which presented the appearance of edematous, fibrous tissue. Inspection of that portion of the lesion situated distal to the incision showed a superficial ulcer of serpiginous outline, covered with a grayish, lardaceous membrane. Tissue for biopsy was removed from the proximal

margin of the infiltrate and the gastrotomy opening closed. The glands along both curvatures in the prepyloric region were enlarged up to 1 cm. in diameter. They were pink and relatively soft; on cross-section of one of them, no tumor deposits were noted. There were a number of scars in the capsule of the liver involving mainly the left lobe. A posterior gastro-enterostomy was performed. In the meantime, the frozen section of the specimen taken for biopsy was reported as showing chronic inflammation with no evidence of carcinoma.

The patient made an uneventful recovery. During convalescence he was placed on antisyphilitic treatment, which was continued until he left the hospital on Aug. 9, 1930. Roentgen examination (fig. 6) of the stomach on Aug. 30, 1930, showed the prepyloric region to be irregularly deformed and the degree of narrowing to be greater than in the original examination. The barium left the stomach mainly through the gastro-enterostomy opening, which appeared to function adequately.

The material removed for biopsy was used for histologic and bacterioscopic examinations and for biologic tests. The testicular inoculation of a saline suspension of the finely divided tissue into two rabbits failed to lead to the development of a scrotal chancre. Dark field examination of a portion of the suspension did not disclose Spirochaeta pallida. Sections stained according to Levaditi contained no demonstrable spirochete.

Microscopic Observations.—Material submitted to Dr. A. S. Warthin was reported by him as follows: "No positive signs of syphilis histologically. Lymph node shows nothing suspicious of syphilis and there is nothing in the scar that would indicate lues. Moreover, spirochete examination is entirely negative." Sections from other areas sent to Dr. Warthin drew the following comment: "Additional material: Chronic inflammation. Fibrosis. Callus of healed ulcer. No evidence of syphilis." Our own description of the histologic preparations of the remaining tissue follows: The wall of the stomach was moderately thickened owing to an increase mainly of the submucous layer. The mucosa showed increased cellularity of the tunica propria. The infiltrating cells were chiefly of the lymphoid type, although eosinophilic leukocytes were relatively abundant. The muscularis mucosae was interrupted and divided by proliferated connective tissue and contained many foci of round cells. The submucosa was several times the normal thickness owing to an increase in the fibrous elements together with infiltrations by scattered and grouped lymphoid and plasma cells. The blood vessels in this layer were increased in thickness, but showed no tendency to obliteration. Occasionally, the infiltrating cells assumed a perivascular arrangement (fig. 7). In general, the walls of the vessels were free from invasion by wandering cells. The muscularis propria supported accumulations of round cells, but was otherwise unchanged. The serous coat was edematous and slightly thickened by virtue of the presence of proliferated connective tissue and infiltration by lymphoid cells.

COMMENT AND SUMMARY

The responsibility of recognizing the presence of syphilis of the stomach at the operating table logically falls on the surgeon. A frozen section made of tissue removed for biopsy during operation is of relatively little aid in establishing a diagnosis of gastric syphilis. The value of the microscopic preparation, provided the block of tissue is properly chosen, lies chiefly in the exclusion of carcinoma. The diagnosis can best be made by a consideration of the gross characteristics of the lesion.

It is on this account that a knowledge of the macroscopic attributes of the condition is of considerable importance to the gastric surgeon.

The features that serve to distinguish syphilis of the stomach from carcinoma, which is most closely simulated, are as follows: There is a striking disparity in many cases between the extent of the lesion as determined roentgenologically and the extent as observed operatively by palpation. Whereas in carcinoma one generally finds at laparotomy a more extensive involvement than the x-ray picture indicates, in syphilis of the stomach there is a surprising paucity or complete absence of changes as determined by palpation. The common lesion of gastric syphilis is not a spherical prominence as in a tumor, gummatous or neoplastic, but is a flat infiltrate that leads to a plaquelike thickening of the gastric wall. When thin, the infiltrate is readily overlooked. When thick, its relatively soft consistency and pliability distinguish it from carcinoma. On cross-section, the increase is seen to be due to an edematous fibrous tissue located chiefly in the submucosa. Inspection of the interior of the stomach generally discloses one or more superficial, serpiginous ulcers involving a large part of the plateau formed by the infiltrate. The base of the syphilitic ulcer, contrary to the peptic variety, is situated at a higher level than the normal mucous membrane. Fibrous and edematous thickening of the serosa and adhesions, when present, suggest an inflammatory rather than a neoplastic lesion. Associated syphilitic changes that may be detected during the course of the operation include hepatic, intestinal and splenic syphilis. Of these, the co-existence in the liver of gummas, deep stellate scars or subtotal destruction of the left lobe is of greatest aid in the recognition of the type of gastric disease present.

In the two cases described here, the gross features of the gastric lesion led to the correct diagnosis in each instance. The first patient was operated on by a surgical colleague who, on palpating the stomach, immediately apprehended that he was dealing with an unusual condition. A verbal description of the physical characteristics led us to predict with confidence that the involvement was syphilitic. The diagnosis in the second case was based chiefly on the observations made at operation, since from biopsy the condition was reported as simple nonspecific inflammation. The associated data, particularly the beneficial effect of antisyphilitic treatment and the subsequent course, lend strong support to the macroscopic diagnosis.

RESECTED KNEE JOINTS

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In spite of advance in knowledge and the great increase in surgical operations with their consequent revelations, there are many diseases of the knee joint that cannot be diagnosed definitely. The study of pathologic specimens which include the entire joint is of significance, but such specimens are relatively rare. The knee joint is seldom examined at necropsy, and various surgical procedures, although affording macroscopic examination, give little material for pathologic research. The operation of resection, however, makes it possible to secure a large enough specimen so that a conception may be formed of the pathologic changes in the joint. The important structures of the joint are all included in such specimens and they can be studied collectively to visualize a definite picture of the changes present. Resection has been performed extensively at the Mayo Clinic for many years, during which valuable data have accumulated.

MATERIAL STUDIED

Records of 236 resections or fusion operations and 9 amputations performed for disease of the knee joint in the years from 1919 to 1931, inclusive, were reviewed. Many of the pathologic specimens were fragmented or incomplete, but 120 were intact, and these were selected. In order to form a basis for comparison in the cases of tuberculosis of the knee joint, the histories of all such cases seen during this same period were reviewed. In 117 cases some type of minor surgical operation was carried out, such as aspiration or cast, and in 139 no treatment was given, patients having been seen in consultation and advised to have treatment elsewhere. A total of 501 case histories was examined.

In 245 cases in which operation was performed, the incidence of trauma or infection as inciting or predisposing factors, the duration of symptoms and the age and sex of the patients were noted. In 168 of these cases (68.6 per cent) tuberculosis was found by microscopic study or by inoculation of guinea-pigs. In 66 cases (27.7 per cent) non-

tuberculous inflammatory lesions were the cause of the destructive process. These cases included the end-results of septic joints, old traumatic joints, extensive proliferative arthritis and old osteomyelitis with involvement of the joints. Nine cases were listed as atrophy; 8 of these were anterior poliomyelitis in which fusion or resection of the knee was performed, and there was a case of painful atrophy due to disuse in which resection had been done. Besides these cases, there were 2 of Charcot's joint.

Of the tuberculous patients, males outnumbered females 2.5 : 1. The ratio in nontuberculous patients, however, was 1.2 : 1. The 2 patients with Charcot's joints were males. The group of patients with atrophy from disuse included 4 males and 5 females. Most of the patients operated on were between the ages of 20 and 40 years; 68.6 per cent were in the tuberculous group, and 57.7 per cent in the nontuberculous group.

ONSET

In 1807, Cooper [1] pointed out the tuberculous predisposition to be noted in many cases and the effect of injury in producing local lesions. Trauma has since been emphasized by many writers as a predisposing factor in disease of the knee joint. Schüller [2] and Krause,[3] who injected the bacillus of tuberculosis into animals, reported that injury to bone and joint tissue was a definite localizing factor. Friedrich,[4] on the other hand, found that traumatized joints were less likely to become involved, and Fraser [5] regarded trauma as of more significance in disseminating disease if a quiescent focus existed, than in localizing the disease primarily. It was his belief that slight trauma localizes a tuberculous process, but that severe trauma causes a reactive state in the tissue which destroys the bacillus of tuberculosis. Salvia [6] stated that trauma in flat bones always determines the site of the lesion, whereas in long bones no definite influence is exerted.

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1. Cooper, Samuel: A Treatise on the Diseases of the Joints, London, R. Phillips, 1807.

2. Schüller, M.: Experimentelle und histologische Untersuchungen über die Entstehung und Ursachen der skrofulösen und tuberkulösen Gelenkleiden, Stuttgart, Ferdinand Enke, 1880.

3. Krause, Fedor: Die Tuberkulose der Knochen und Gelenke, Leipzig, F. C. W. Vogel, 1891.

4. Friedrich, P. L.: Experimentelle Beiträge zur Kenntnis der chirurgischen Tuberkulose, Deutsche Ztschr. f. Chir. **53**:512 (Nov.) 1899.

5. (a) Fraser, John: An Experimental Study of Bone and Joint Tuberculosis, J. Exper. Med. **17**:362 (March) 1913. (b) Tuberculosis of the Bones and Joints in Children, London, A. & C. Black, Ltd., 1914.

6. Salvia, Edoardo: L'influenza dei piccoli traumi sulla localizzazione della tuberculosi, Policlinico (sez. chir.) **11**:367, 1904.

In our series of cases, only 39.8 per cent of the patients with tuberculosis and 39.4 per cent of those without tuberculosis gave a history of previous injury which might in any way have been an inciting cause. Such injuries varied from a slight bruise to a fall from a telephone pole. Practically the same percentage of traumatic background was presented by male and female patients, which suggests that the severity of the injury matters little so far as a predisposing factor is concerned. Some writers are definitely of the opinion that slight sprains or bruises are more likely to be localizing factors than fractures or dislocations.

TABLE 1.—*Onset of Disease*

	Tuberculous		Nontuberculous Arthritis	
	Cases	Per Cent	Cases	Per Cent
Trauma				
Total	67	39.8	26	39.4
Male	48	40.6	16	44.4
Female	19	38.0	10	33.3
Following Infection	8	4.7	12	18.2
Idiopathic	93	55.4	28	42.4

TABLE 2.—*Infectious Type*

	Tuberculous	Nontuberculous
Following		
Typhoid fever	1	1
Scarlet fever	1	..
Osteomyelitis	..	3
Pneumonia	2	..
Gonorrhea	..	2
Rheumatic fever	..	2
Influenza	1	1
Influenza, scarlet fever and tonsillectomy	1	..
Scarlet fever and typhoid fever	..	1
Measles and bronchitis	1	..
Encephalitis	..	1
Tonsillitis	..	1
Lymphangitis of leg	1	..

Four and seven-tenths per cent of the patients with tuberculosis and 18.2 per cent of those without tuberculosis were observed from a few days to several months after some form of acute infection had been manifested elsewhere in the body (tables 1 and 2). It may be noted that *in 5 of the 8 cases of tuberculous arthritis with preceding acute infection, the condition followed a respiratory disease, whereas in only 1 of the 12 cases in which tuberculosis was not present was this true.*

DURATION OF THE DISEASE

In 55.8 per cent of all cases the disease had existed prior to operation more than five years. The shortest duration of symptoms in the tuberculous cases was three months, the longest, thirty-nine years. and in the nontuberculous cases, four months and thirty-three years.

respectively. Patients with Charcot's joints gave a history of duration of five and two years.

In the 256 cases in which tuberculosis was present and operation was not performed, variation from these figures was noted only in age incidence and duration. The proportions of males and females were the same, and the percentage of cases in which inciting trauma was apparent was even lower, 36.6 per cent. In this group only 35.8 per cent of the patients were between the ages of 20 and 40 years; the majority, 50.3 per cent, were in the first two decades of life. The youngest patient was aged 14 months and the oldest 73 years. In only 25.6 per cent of this group of cases was the duration of the disease more than five years; the shortest duration was two weeks, and the longest was more than thirty years. These facts seem to show that age was an important factor in the selection of cases for operation. Only 0.6 per cent of the patients in the operative group were aged less than 11 years, as compared with 30.9 per cent of those not operated on. Furthermore, the higher incidence of short duration of symptoms among patients not operated on reveals the tendency to avoid radical procedures as long as possible with the hope of relief by some other means. This is most striking when the duration was one year or less; there were 30.2 per cent of these patients among those not operated on, as compared with 5.3 per cent among those who were operated on.

GROSS SPECIMENS

From 245 cases in which operation was performed, 120 whole specimens were obtained. These included the articular surfaces of the tibia, most of the articular surfaces of the femur, varying amounts of synovial membrane, and in more than half of the cases, the entire patella. One hundred and two of the specimens were tuberculous, 17 were nontuberculous and 1 specimen was a Charcot joint. Since the clinical symptoms had existed from three months to thirty-nine years, the pathologic changes in the specimens were varied. In some cases there was marked destruction of all the structures of the joints. In others the tissues were practically intact. In comparing the specimens and histories, we found the progress of the nontuberculous types of infection more rapid than the tuberculous type as a general rule. This same observation was made by Koenig[7] in 1884. His work on the subject of tuberculosis of bones and joints has received widespread corroboration and but little significant contradiction.

As a rule, in cases of tuberculosis of short duration of symptoms, there is only slight pathologic change; usually early pannus formation

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7. Koenig, Franz: Die Tuberculose der Knochen und Gelenke, Berlin, A. Hirschwald, 1884.

is present, or slight invasion of margins of bone. The cartilage is intact in most cases. In the cases in which tuberculosis is not present there is, as a rule, advanced change in the structures of the joint, particularly the cartilaginous structures, with some destruction of bone (figs. 1 and 2). In advanced cases marked destruction may accompany both types of infection, and they are often indistinguishable grossly. Exceptions, however, are not uncommon. In several cases of tuberculosis of long duration there was little destruction. In one case, in which the clinical history covered more than fifteen years, only the

Fig. 1—Tuberculous joint of three years' duration.

external surfaces were affected (fig. 3). This illustrates the ability of tuberculosis to become walled off almost completely in one compartment of a joint, destroying that part and leaving the remainder fairly free. Certain specimens, however, disclosed much more rapid progress of the disease in the cases in which tuberculosis was present and slow progress in those in which it was not present. In a case in which tuberculosis was not present, only the external surfaces were involved after twenty-two years of symptoms.

The question of whether the site of origin of tuberculosis of the joint is in the synovia or bone has been discussed for many years.

Berry[8] stated that most older writers, including Billroth, favored a synovial origin, whereas Volkmann, Schüller, Virchow and several others felt that the primary lesion was in the bone. More recently, Fraser[5b] has advanced the opinion that tuberculosis of the joint is definitely synovial in origin. Rogers,[9] Stiles[10] and Smith[11] believe this to be true in the majority of cases. Nichols,[12] on the other hand, thought that a focus in bone existed in every one of his specimens. Koenig[7] stated

Fig. 2—Nontuberculous specimen of one year's duration (compare with fig. 1).

8. Berry, J. J.: Articular Osteitis of the Knee in Children, M. Rec. **17**:113, 1880.

9. Rogers, M. H.: Tuberculosis of the Knee-Joint in Adults, Am. J. Orthop. Surg. **12**:589 (April) 1915.

10. Stiles, H. J.: The After-Results of Major Operations for Tuberculous Disease of the Joints, Brit. M. J. **2**:1356 (Nov. 16) 1912.

11. Smith, A. DeF.: The Pathology of Joint Tuberculosis in Its Earlier Stage, Arch. Surg. **12**:740 (March) 1926.

12. Nichols, E. H.: Tuberculosis of Bones and Joints, Tr. Am. Orthop. A. **11**:353, 1898.

that the origin might be either in bone or synovia; Ely [13] and Phemister [14] also adopted this view. In 56 per cent of our gross tuberculous specimens the process was advanced, both in bone and synovial membrane, so that it was impossible to ascertain the primary site. Of the remaining specimens, 37.2 per cent appeared to be primarily in the synovial membrane, whereas only 6.8 per cent disclosed evidence of a primary lesion in the bone. The distinction is difficult and, as will be shown, is of little

Fig. 3—Tuberculous knee of fifteen years' duration. There is destruction of the external surfaces and the patella. The cartilage of the internal surfaces is well preserved.

practical significance. In all of our specimens both synovial membrane and bone were involved, so that from the surgical standpoint tuberculosis was not limited to either bone or synovial membrane; undoubtedly

13. Ely, L. W.: Joint Tuberculosis, with Special Reference to Its Pathology, M. Rec. 76:551 (Oct. 2) 1909.

14. Phemister, D. B.: Changes in the Articular Surfaces in Tuberculous Arthritis, J. Bone & Joint Surg. 23:835 (Oct.) 1925.

this may occur, but almost invariably it is before a diagnosis can be made. When tuberculosis becomes sufficiently advanced to make possible a clinical diagnosis, it has spread to both structures. Pasquali,[15] in a recent report of 156 resections of the knee at the Instituto Rizzoli, mentioned 3.8 per cent as purely synovial in origin, 3.2 per cent as in the bone and 93 per cent as osteo-arthritic.

In 94.1 per cent of the cases in which tuberculosis was not present, the lesion appeared to be of synovial origin. In only a single case was there question of a focus of infection in bone. In all cases opinion was based on the condition of the articular surfaces, the appearance of the cut surfaces and the condition of the bone as seen by sections through the surfaces of the joint.

Various writers have observed certain sites of predilection for the origin of tuberculosis. Ely[16] stated that the head of the tibia is the most common starting point. Fraser[17] thought the lower end of the femur was the most common primary site of the disease. Kolodny[18] believed the external epicondyle to be the favorite site because of its more extensive circulation. Henderson[19] noted that it is not extremely rare to find the disease originally in the patella. In 52.6 per cent of our tuberculous specimens, the site of the primary lesion could not be determined. In 34.4 per cent the site was apparently in the tibia, in 10 per cent it was in the femur and in 3 per cent in the patella. In the nontuberculous specimens the point of origin seemed to be equally distributed between the tibia and the femur; the patella was primarily involved in a case. Because of the rapid progress of the disease, it was difficult to ascertain the primary site.

It is the general belief that in the presence of inflammatory lesions of the joints, cartilage is never primarily affected but is passively invaded and destroyed by surrounding disease. In studying the tuberculous specimens, we found that the cartilage seemed to be attacked from three sources: (1) the overlying pannus formation springing from the synovial membrane at the margins; (2) the subchondral granulation tissue spreading along beneath the cartilage and usually arising from

15. Pasquali, E.: Esiti della resezioni viella tubeculosi del ginocchio, Bibliog. Orthop. **11**:193 (June) 1931.

16. Ely, L. W.: Joint Tuberculosis, New York, William Wood & Company, 1911.

17. Fraser, John: Observations on the Situation of the Lesions in Osseous Tubercle, Edinburgh M. J. **9**:436 (Nov.) 1912.

18. Kolodny, Anatole: A Contribution to the Knowledge of Pathogenesis of Skeletal Tuberculosis, J. Bone & Joint Surg. **23**:53 (Jan.) 1925.

19. Henderson, M. S.: Tuberculosis of the Knee Joint in Children, Minnesota Med. **3**:463 (Oct.) 1920.

the margins of the surface of the joint, at times lifting the cartilage free of the bone and at times perforating the cartilage, and (3) the destruction taking place through erosion of the surfaces of the joint chiefly at the areas of pressure. In the nontuberculous specimens pannus formation was slight, the cartilage apparently being destroyed chiefly by the effect of pressure or by digestion due to toxic products of infection within the joint, or by both of these factors. In the tuberculous specimens the persistence of portions of the cartilage over many years was often observed. In the nontuberculous specimens, however, whenever cartilage had been destroyed, it had been removed and replaced by fibrous tissue, or ankylosis was present in various stages of activity.

Phemister [20] demonstrated the basis for these different reactions. In our tuberculous specimens there was good preservation of cartilage in 16.6 per cent of the cases, destruction of varying severity in 80.4 per cent and only partial involvement of the surfaces in 3 per cent. In the nontuberculous specimens there was fairly good preservation in 11.7 per cent, destruction (usually more severe than in the tuberculous specimens) in 70.6 per cent and only partial involvement in 17.7 per cent. In the nontuberculous specimens destruction was always greater at the areas of pressure of the surfaces of the joint. This corroborates the observations of Phemister, who found that the cartilage attacked by proteolytic ferments of the exudate of the joint is vulnerable to the pressure from the opposite surface of the joint and the most extensive erosion takes place at this point. In tuberculosis, however, he found a marked scarcity of these proteolytic ferments, which might account for the slow progress of the disease and the preservation of cartilage at the areas of pressure.

In our tuberculous specimens, there was no definite rule as to the point of greatest destruction of cartilage. Koenig [21] first expressed the opinion that in tuberculosis the cartilage is destroyed chiefly at areas where pressure is absent. According to Phemister, [14] "articular cartilage may be affected: (1) by the direct action of tubercle toxins, (2) by tuberculous granulation tissues and (3) by the pressure erosion in opposing articular surfaces." He explains the growth of the pannus over the surface of the joint, the areas of pressure being kept clear of pannus by friction, but as the joint becomes more involved and less motion takes place more of the auricular surface becomes covered. Phemister has shown how, in severe cases, there may be two types of

20. Phemister, D. B.: The Effect of Pressure on Articular Surfaces in Pyogenic and Tuberculous Arthritides and Its Bearing on Treatment, Ann. Surg. **80**:481 (Oct.) 1924.

21. Koenig, Franz: Die Tuberculose der Knochen und Gelenke, Berlin, A. Hirschwald, 1896.

change which greatly alter the picture from that which is seen in the less severe forms, i. e.:

First, there may be caseation of the tuberculous granulations, and those overgrowing the surfaces of the articular cartilage are equally affected with those involving the synovial membrane. This early caseation may either entirely prevent the overgrowth of granulations on the cartilage or rapidly remove those that have formed, so that destruction by direct attack of tuberculous tissue along the free surface of the cartilage is either limited in amount or entirely lacking. A second effect of severe tuberculous arthritis may be the production of necrosis of large areas of articular cartilage, partly by the action of the tubercle toxins and partly by cutting off of nutrition from the normal synovial fluid. . . . When the infec-

Fig. 4.—Tuberculous knee of ten years' duration. Marginal pannus formation and cartilaginous destruction with preservation at the areas of pressure are shown.

tion is sufficiently severe to kill articular cartilage, it may do so in the regions of contact and pressure of opposed articular surfaces, as is the case in severe pyogenic arthritis.

Our specimens have demonstrated that the preservation of cartilage at the areas of pressure cannot be depended on as a diagnostic factor in favor of tuberculosis of the knee (figs. 4 and 5). In 29.4 per cent of the cases there was greater destruction of cartilage at the margins of the joint. In 20.6 per cent the destruction was definitely greater at the areas of pressure. In 44.1 per cent distinction could not be made because of advanced destruction, while in 5.9 per cent the different surfaces of the

joint presented dissimilar changes, some showing greater destruction at the center and others at the periphery.

The comparatively large number of cases in which there was central destruction suggested that prolonged weight-bearing might be a cause of the variation. Examination of the histories disclosed that about half of the patients had been receiving treatment designed to relieve the effect of weight-bearing. Approximately the same proportion of

Fig. 5.—Tuberculous knee of one year's duration. Destruction of cartilage at the areas of pressure and contact with preservation at the margins are shown. A tuberculous pannus has extended across the external condyle just above the pressure.

exposure to pressure existed in the presence of destruction of margins, so that this factor was probably not responsible for the divergent cartilaginous changes.

In 85.2 per cent of the cases in which there was greater marginal destruction, the pannus was nodular and luxuriant; it was caseous in 7.4 per cent and fibrous in 7.4 per cent. The original lesion was apparently synovial in 70.3 per cent and questionable in 29.7 per cent. In 45 per

cent of the cases of greater central destruction, the pannus was nodular and luxuriant; it was caseous in 25 per cent, fibrous in 5 per cent and entirely absent in 25 per cent. The original lesion was apparently synovial in 55 per cent, bony in 5 per cent and questionable in 40 per cent.

There are several possible reasons for the increased destruction at areas of pressure. As Phemister has claimed, there is a higher percentage of cases of central destruction with caseous pannus than of marginal destruction; this means less peripheral destruction and greater toxicity of joint fluid with less resistance of the central cartilage to pressure. The number of cases in which there is no pannus formation is significant. Ordinarily the marginal pannus forms a peripheral cushion which receives part of the weight from the opposing surface of the joint, and tends to relieve the strain on the area of pressure. When it is absent, the central area is in no way protected from the effects of pressure and subchondral disease. Finally, a greater percentage of questionable foci in bone in cases of central destruction may be of some significance. The effect of the subchondral changes will be considered under microscopic sections. In our nontuberculous specimens there was pannus formation in only 2 cases (12 per cent). These were firmly attached to the surface of the joint. In the tuberculous specimens it was seen in 35 cases (34.3 per cent). The pannus was attached only to the synovial reflection in half of these cases; in the remainder it was closely adherent to the cartilage. In 16.6 per cent of the tuberculous specimens abscess of bone was present; it was present in the tibia in 12.7 per cent, in the femur in 1 per cent and in both bones in 2.9 per cent.

The presence of sequestrums in tuberculous joints has been recognized by many writers and noted with varying frequency. In 29 cases (28.4 per cent) we observed these either as bits of bone more or less detached, or more frequently as areas of eburnated bone along the surface of the joint; they were seen in the tibia in 5.9 per cent, in the femur in 6.8 per cent and in both bones in 15.7 per cent. Usually these areas of sequestration were easily seen. In several instances, however, they were completely covered with cartilage and were only discovered by inspection of the cut surface of the bone or by making a section through the joint. Ordinarily such cartilage was badly destroyed but in 1 specimen, an early case, it was apparently intact. Sequestrums appeared in areas of pressure in all except 2 cases, and in these it is possible that the area of pressure had been shifted somewhat, owing to the relaxation of the capsule of the joint. In 13 cases (12.7 per cent) we observed the presence of "kissing sequestrums," or opposing areas of sequestration, in the tibia and femur. Of these, 2.9 per cent

were on the internal surfaces, 8.8 per cent on the external surfaces and 1 per cent was on both the internal and external surfaces. All of these occurred on areas of pressure. In the nontuberculous specimens only 1 sequestrum was found. This was in the external tuberosity.

All of the surfaces of the Charcot joint contained hypertrophied bone. The articular cartilage was entirely absent except in spots at the periphery where some fibrocartilage still remained. The ends of the bones were extensively eburnated, but sequestrums were not observed. Several questionable loose bodies were seen in the fibrous attachment to the tibial tuberosity. No vestige of the capsule of the joint or ligamentous structure remained. The picture was one of advanced destruction of soft tissue with overgrowth of bone.

ROENTGENOGRAMS

A review of the roentgenograms available in these cases showed that again there are many exceptions to the usually accepted rules. One is led to believe that in tuberculous joints there is a characteristic picture of haziness or cloudiness, with later erosion of margins and preservation of the joint space. In the final stages advanced destruction of bone may be evident. Atrophy of bone is usually considered an essential accompaniment of tuberculosis of the joint. In the nontuberculous joint early obliteration of the joint space often with ankylosis of bone is the more commonly accepted picture.

We found it difficult in the early cases to pick out any constant diagnostic features in the roentgenogram which could be said to identify either type of lesion. In the advanced cases again marked difference did not exist, but in the moderately advanced cases changes were found to be more typical. In all cases in which changes are apparent in the roentgenograms the disease is probably well advanced. In cases of tuberculosis the disease is usually well advanced, as far as any hope of checking its spread throughout the joint is concerned, before the patient consults a physician. In cases of nontuberculous infections a more marked change may be seen in a relatively shorter time, but this time period is often too prolonged to make the roentgenogram of very great value as an aid to early diagnosis. In 77 per cent of the tuberculous specimens the roentgenograms disclosed atrophy; hypertrophic changes were apparent in 12.3 per cent, and there was no change in density of bone in 10.7 per cent. In 63.7 per cent of the nontuberculous cases the roentgenograms disclosed atrophy; hypertrophic changes were present in 18.2 per cent. No change was observed in 18 per cent of the cases.

As an index to diagnosis the intact joint space must be regarded with some reservation. Often there is flexion contracture in the knees.

and the joint space cannot be truly represented in the roentgenogram. In most of our cases there was greater destruction of cartilage in the nontuberculous joints for a given duration of symptoms. Compared with the gross specimens there was only a small percentage (9.3 per cent) in the tuberculous cases in which roentgenograms failed to demonstrate cartilaginous changes. In 45.4 per cent of the nontuberculous joints, however, the roentgenograms demonstrated less change than was actually present. From the standpoint of destruction of bone, roentgenograms of both tuberculous and nontuberculous specimens disclosed more than was seen on superficial inspection of the gross specimen. This is due to the subchondral erosion of bone which takes place at the margins of the joint in many cases before the cartilage has been removed. Many areas of destroyed bone are covered by dense pannus or filled with tuberculous granulation tissue so that they are not seen on inspection of the gross specimen unless it is sectioned. Erosion of margins may be seen in nontuberculous specimens so it is not a diagnostic sign in tuberculosis. There was greater destruction apparent in roentgenograms of areas of pressure than at the margins in a large percentage of the tuberculous as well as of the nontuberculous joints. The roentgenograms failed to reveal sequestrums when they were present in a considerable number of cases. Of 20 tuberculous joints with sequestrums in the gross specimens only 7 (35 per cent) were visible in the roentgenograms. Thus too much stress cannot be placed on the interpretation of the roentgenologic findings alone. The roentgenogram is, of course, an essential adjunct to diagnosis, but taken alone it may in many cases be inconclusive and even misleading.

MICROSCOPIC SECTIONS

Sections were cut through the surfaces of joints of the complete specimens in 91 tuberculous joints, in 15 nontuberculous joints and in 1 Charcot's joint. Three types of changes were investigated in all cases, namely, bony, synovial and cartilaginous. Actual section of the tissues of the joint results in the smallest amount of error. The microscopic appearance of tuberculosis has been definitely demonstrated. When inflammatory tissue is present, without collections of epithelioid cells and lymphocytes, then tuberculosis cannot be diagnosed. Giant cells are not necessary for the diagnosis. In fact, foreign body giant cells are often present, acting as osteoclasts or chondroclasts in tissues that are definitely not tuberculous. Unfortunately, since tuberculosis usually spreads slowly, specimens removed from the joint for examination may not contain the lesion, whereas in another portion of the joint the disease may be rampant. In several cases, specimens diagnosed as nontuberculous at the time of operation were found on further investigation of

other areas of the joint to be tuberculous. On the other hand, in many cases in which the pathologist had diagnosed tuberculosis, additional sections were necessary in order to establish the pathologic change. In all diagnostic explorations, therefore, it is necessary to take a goodly amount of tissue for examination, and preferably from many portions of the joint.

Our sections of tuberculous tissue demonstrated the typical lesions, whether nodular, caseous or fibrous. There was evidence in all of the
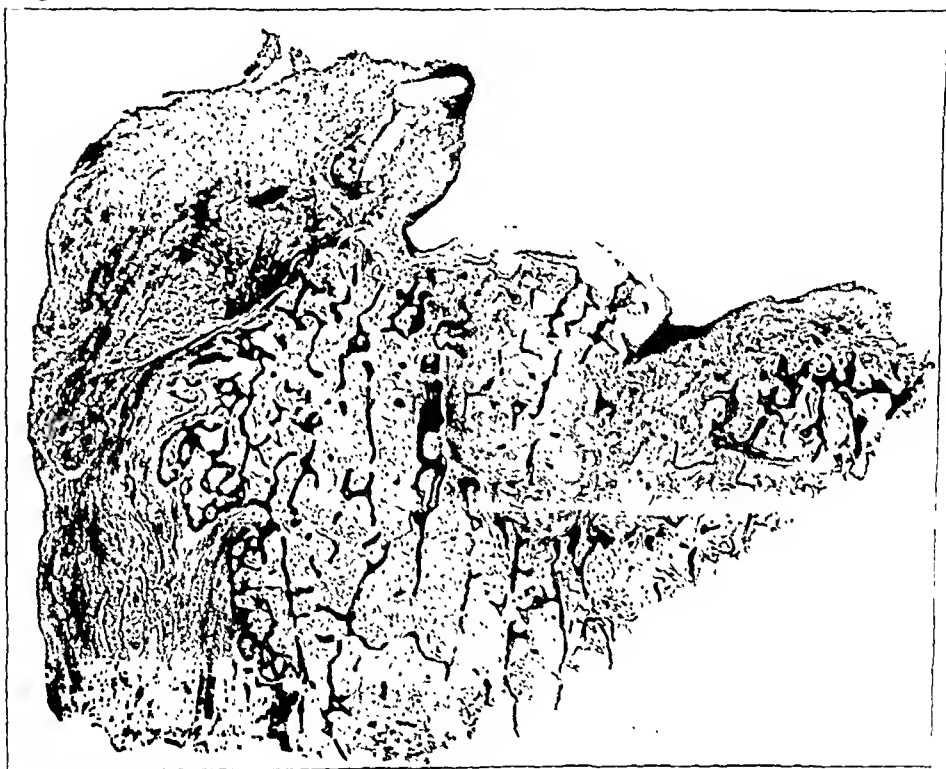
Fig. 6.—Tuberculous subchondral granulations springing from the margins of the joint and dipping down to surround a sequestrum, over which the dead cartilage still remains.

sections of involvement of both synovia and marrow. Therefore, we feel that the distinction between tuberculosis of synovia and bone is futile from a practical point of view. In cases in which the origin was evidently synovial and in which grossly the surface of the joint was almost intact there was marginal infiltration of the marrow and definite invasion of granulation tissue beneath the cartilage. In cases in which the origin appeared to be primarily in the bone, some spread of the infection to the synovial reflection at the margin of the joint was almost invariably present.

Cartilage in all sections appeared to be invaded secondarily. In some cases this was due to a focus in the bone beneath the cartilage eroding and possibly perforating from beneath. Usually, however, it occurred secondarily to marginal involvement of the synovia, either in the form of a tuberculous pannus creeping over the surface of the joint, or as subchondral granulation tissue spreading between bone and cartilage and destroying slowly as it progressed.

The nontuberculous sections manifested little evidence of pannus formation. When present, it was fibrous and adherent. In most cases the cartilage was entirely destroyed and replaced by fibrous tissue. In 40 per cent of the cases subchondral granulation tissue, consisting of fibroblasts, round cells and young capillaries were present between the bone and the cartilaginous remnants. These nontuberculous sections suggested a primary synovial lesion in all cases. In 66.6 per cent of cases there was atrophy of bone. In 20 per cent there was no change, and in 13.4 per cent there was hypertrophy of bone.

In the tuberculous sections the cartilage was fairly well preserved in 13.2 per cent of cases; the remainder showed all grades of degeneration and replacement by fibrous tissue. The bone itself was atrophic in 60.4 per cent of cases and hypertrophic in 3.3 per cent. In 4.4 per cent there was definite abscess formation, in 26.3 per cent sequestrums were present and in 5.6 per cent change was not demonstrable. Of the 24 cases in which microscopic sequestrums were found, they were visible in only 16 of the gross specimens. In 16.6 per cent of the cases pannus formation was not observed. Of those present, 60 per cent were nodular, 11.27 per cent were fibrous and 11.7 per cent were caseous.

Most writers have claimed that subchondral granulations in tuberculous tissue, except at the very margins, show no evidence of tuberculosis. Phemister stated that the tissue is a reaction of foreign body granulation to the degenerated cartilage lying above in an effort to remove it completely. In 58.2 per cent of our sections subchondral granulation was not present. In 29.7 per cent of the cases the subchondral granulations were nonspecific, consisting of fibroblasts, round cells and young capillaries with occasional foreign body giant cells. In 12.1 per cent the tissue was clearly tuberculous in the center of the joint. In several of the cases in which the granulations were classified as nontuberculous, the tissue was of questionable nature, having many of the characteristics of tuberculous tissue without definite cellular arrangement.

Sequestrums were, in some cases, due to foci in bone beneath the cartilage. In others they were apparently due to subchondral granulations dipping down to surround an area of bone, most commonly at an area of pressure (fig. 6). In only one or two instances were sequestrums found at areas where pressure was absent.

In all cases there was either no cartilage over a sequestrum, or the cartilage was fibrillated and dead. This dead cartilage invariably was eroded from opposing pressure, except those occurring at the margins. In all except one case there were no subchondral granulations in an area of sequestration.

In the cases in which there was greater destruction of cartilage at areas of pressure, there was either a sequestrum causing loss of nutrition of the cartilage or a luxurious growth of subchondral granulation tissue; in 40 per cent of the cases this was tuberculous. There seemed to be no hard and fast rules for the microscopic appearance of the lesions, just as we had observed in the gross specimens and in roentgenograms. The changes due to tuberculosis differed considerably in the various specimens. By and large, however, the microscopic examination was by far the most satisfactory.

Sections of the Charcot joint contained a small amount of fibrocartilage covering hypertrophic dense bone. There was considerable formation of new bone and a good deal of osteoid tissue. Fibrosis was present in the marrow spaces near the joint. The cellular elements consisted of a few scattered fibroblasts and round cells. Subchondral granulation tissue was not present.

DIAGNOSIS

The clinical diagnosis of the two principal types of arthritis of the knee under consideration is sufficiently difficult to involve a large percentage of error. In a recent article Milgram [22] has shown that in a fairly large group of proved cases of tuberculosis of the bones and joints, 38.7 per cent were incorrectly diagnosed clinically. Of the unrecognized conditions, 67.3 per cent were not diagnosed by the operators as tuberculous from the gross appearance. One of us (Ghormley [23]) published a similar report in a review of 135 cases of disease of the joints. In 41 cases a diagnosis of tuberculosis was made clinically. In only 66 per cent was this ultimately found to be correct. In 42 cases a diagnosis was made of nontuberculous arthritis. The final diagnosis by examination of tissue in this group was tuberculosis in 38 per cent. Hibbs and von Lackum,[24] Ely [25] and Friedrich [26] reported similar figures.

22. Milgram, J. E.: Diagnostic Inaccuracy in Tuberculosis of Bone, Joint and Bursa, J. A. M. A. **97**:232 (July 25) 1931.

23. Ghormley, R. K.: Joint Disease, J. Bone & Joint Surg. **24**:858 (Oct.) 1926.

24. Hibbs, R. A., and von Lackum, H. L.: End-Results in the Treatment of Knee Joint Tuberculosis, J. A. M. A. **85**:1289 (Oct. 24) 1925.

25. Ely, L. W.: Further Observations on the Pathology of Joint Tuberculosis and Practical Deductions Therefrom, M. Rec. **78**:147 (July 23) 1910.

26. Friedrich, H.: Ueber Fehlerquellen der exakten Untersuchungsmethoden zum Nachweis von Tuberkulose und Aktinomykose, München. med. Wchnschr. **77**:1443 (Aug. 22) 1930.

In our group of 168 cases of proved tuberculosis, 75.6 per cent were correctly diagnosed clinically; in 13.6 per cent tuberculosis was considered as a possibility, and in 10.8 per cent the diagnosis of nontuberculous arthritis was made. Of the 66 cases of proved nontuberculous arthritis, 86.3 per cent were so diagnosed preoperatively, while 13.7 per cent were diagnosed as tuberculous.

Insidious onset, slow progress and frequent remissions and exacerbations point toward tuberculosis as the causative factor. Prolonged drainage from a joint without signs of acute inflammation is probably in favor of tuberculosis, but drainage itself is not diagnostic. In 11.3 per cent of our cases of tuberculosis there had been drainage for variable periods. It should be emphasized here that prolonged drainage in a case of tuberculosis usually means secondary infection, and such secondary infection, in most instances, so modifies the histologic picture as to make tuberculosis almost unrecognizable. Nineteen and seven-tenths per cent of patients without tuberculosis gave a history of drainage. Except in the cases of osteomyelitis with involvement of joints, the drainage of tuberculous material was more prolonged. The finding of tuberculosis elsewhere in the body may be helpful in the diagnosis. However, one of our patients had active pulmonary tuberculosis but the affected joint was not tuberculous. Ankylosis of bone demonstrated by the roentgen ray is definitely against tuberculosis, unless there has been secondary infection. Nevertheless, in many cases there are few clinical data for accurate differentiation.

The tuberculin test, although it has its enthusiastic proponents, cannot be considered a dependable diagnostic measure, especially if patients are adults. A negative reaction is of more significance as being against a diagnosis of tuberculosis. In 7.6 per cent of our nontuberculous cases, there was involvement of one other joint; in 21.2 per cent there was multiple involvement of joints, resembling that seen in the ordinary type of proliferative arthritis. In 13.1 per cent of the cases of tuberculosis one other joint was affected, while in 5.4 per cent mulitple joints were affected. Roentgenograms and specimens demonstrated the great difficulty of accurate diagnosis by the roentgen ray or by mere visualization at the time of exploration.

Inoculation of guinea-pigs is considered by many investigators to be an accurate diagnostic measure. The idea is not recent. Senn,[27] in 1887, quoted Tavel in the opinion that, when the distinction between tuberculosis and syphilis cannot be made clinically or by the microscope, inoculation experiments always give positive and reliable information. Recent

27. Senn, Nicholas: Four Months Among the Surgeons of Europe; A Series of Letters to Dr. Christian Fenger. Reprinted from J. A. M. A., 1887, vols. 8 and 9, Chicago, 1887.

opinions have varied as to the value of the procedure. Krause [28] stated: "The inoculations of guinea-pigs with suspected material for the diagnosis of tuberculosis should, in my opinion, rank as high in reliability as any laboratory procedure which we have." On the other hand, Smith,[29] in 1924, reported a series of 18 cases in which tuberculosis was found at the time of operation. Of these, the results of inoculation of guinea-pigs were positive in 10 and negative in 4. In 2 cases the pigs died too early for diagnosis, and in the remaining 2 the reports could not be traced. In a recent publication, Sundt [30] reported that in 25 per cent of his cases the results of inoculation of guinea-pigs were negative, but tuberculosis was found on microscopic examination of the tissue. In our cases, unfortunately, only 24 such inoculations were made. In 21 cases the results agreed with the microscopic data, 20 were positive and 1 was negative. In 3 cases the results of inoculation were negative, but the diagnosis of tuberculosis was made by examination of tissue. The error, therefore, in the results of inoculation of guinea-pigs was 12.5 per cent.

MICROSCOPIC DIAGNOSIS

There remains, then, the evaluation of microscopic examination as a method of diagnosis. Without doubt this method is not devoid of inaccuracy. At times there may be some contraindication to arthrotomy. Then again, as has been pointed out, the disease may be localized to one area of the joint, and unless generous and multiple specimens are sent to the laboratory the lesion may be overlooked. Furthermore, in cases of secondary infection it is extremely difficult to recognize the characteristic lesions, which appear greatly attenuated by the superimposed pathologic change and may even be entirely unrecognizable. It may be that in such cases inoculation of guinea-pigs will demonstrate what cannot be seen in the original tissue, but we had no opportunity to investigate this possibility.

In our series of 126 cases in which the pathologist diagnosed tuberculosis at the time of operation, we were able in every instance to confirm the diagnosis from examination of tissue of the preserved specimens, although in 22 cases additional sections were necessary in order to demonstrate the lesion. In the other 42 cases of this group microscopic sections were not made. Of the 66 nontuberculous specimens, 32 which had been so diagnosed at the time of operation were sectioned and reexamined; in 5 of these tuberculosis was definitely demonstrated.

28. Krause, A. K., quoted by Ghormley.[23]

29. Smith, A. DeF.: The Early Diagnosis of Joint Tuberculosis, J. A. M. A. 83:1569 (Nov. 15) 1924.

30. Sundt, Halfdan: The Diagnosis and Frequency of Tuberculous Disease of the Knee, J. Bone & Joint Surg. 29:740 (Oct.) 1931.

Therefore, in the entire group of 158 microscopic sections, there was a pathologic diagnostic error of 3.2 per cent.

SUMMARY

The clinical history, roentgenograms, lesions discovered grossly and microscopically and results of inoculation of guinea-pigs in a series of 236 resections and 9 amputations of the knee joint have been studied.

The preoperative diagnosis was found to be incorrect in 24.4 per cent of the cases of tuberculosis and in 13.7 per cent of the cases of nontuberculous arthritis.

The gross specimens and roentgenograms were found to vary so widely as often to prevent the possibility of accurate diagnosis.

The inoculation of guinea-pigs proved incorrect in 12.5 per cent of the 24 cases in which inoculation was made.

The diagnosis made by microscopic examination of tissue removed at the time of operation has been found to be accurate in all but 3.2 per cent of the cases, an error of omission.

"ORBITAL INCLUSION" CYSTS AND CYSTO-ADENOMAS OF THE PAROTID SALIVARY GLANDS

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Cystic growths sometimes occur in the parotid salivary gland; they are lined with stratified epithelium, usually of the cylindric type, and rest on a base of lymphoid tissue. The latter is generally hyperplastic, and its growth either makes the lining appear papillated or, if it is extreme, fills the whole cyst with epithelial-clad lymphoid nodules. In the latter event the epithelium generally proliferates and forms small acini, and the growth assumes the pattern of a cystic adenoma. Sometimes, as in Cunningham's [1] case, the cysts are multiple. The epithelium is described by some authors as ciliated but more frequently as nonciliated. The cysts have appeared in persons of all ages from 12 to 74 years, have been twice as frequent in men as in women and are generally situated in the lower pole of the gland. Usually there are no symptoms except swelling with occasional twinges of pain unless there is infection. This can lead, as in other epithelial-lined cysts, to the formation of persistent sinuses. Removal of the cyst and all its lining will cure the condition.

The chief interest in these growths lies in the riddle of their origin. Although forming in adult life as a rule, it seems obvious that they must come from some developmental fault, for they are composed of tissues not found in the normally developed parotid gland.

We have had an opportunity to study three of these cysts—one reported by Cunningham,[1] one reported by Hanford [2] and one unpublished case. A perusal of published cases showed that there have been offered almost as many different explanations of their origin as there have been authors. This confusion led us to review the investigations of the embryology of the region of the anlage of the parotid gland, and

1. Cunningham, W. F.: Ann. Surg. **90**:114, 1929.

2. Hanford, J. M.: Branchiogenic Adenoma of the Neck, Ann. Surg. **94**:461, 1931.

as a result we have found, especially in the researches of Schulte,[3] what seems to be a satisfactory explanation for the cysts in a structure known as the "orbital inclusion." This gives rise to the orbital salivary glands in some of the carnivora and appears as a vestigial rudiment in human embryos.

REPORT OF CASES

CASE 1.—*History.*—R. M., a man, aged 61, a postoffice clerk, noticed a small mass at the angle of the left jaw for two years before coming to the hospital. It was entirely symptomless at first, but later gave slight twinges of pain. It did not interfere with mastication. Examination revealed an ovoid mass about 5 cm. in diameter directly over and somewhat behind the angle of the jaw. It was resilient but not definitely cystic. The skin was freely movable over it, but the mass was attached to the deeper structures. The patient also had a slight enlargement of the right lobe of the thyroid and suffered from chronic myocarditis and emphysema.

Operation (Aug. 15, 1930, by Dr. John M. Hanford [2]).—With the patient under intranasal ether anesthesia, a curved incision 6 cm. long was made from the lobe of the ear downward and forward exposing the tumor in the parotid region. It was well encapsulated and was removed by sharp and blunt dissection. When the tumor was removed from the anterior portion two or three drops of what appeared to be pus escaped, but no abscess cavity was found. One goiter tube drain was inserted.

Course.—The wound drained purulent exudate for six days. Staphylococcus albus was obtained on culture. The patient was discharged the seventh day with slight induration about the wound. No evidence of infection was present after two weeks. After seven months there was apparently no reappearance of the lesion.

CASE 2.—*History.*—D. L., a woman, aged 74, had noticed a small tumor below and in front of the left ear four years before coming to the clinic. Two years later it began to grow noticeably larger and to extend backward. During this time it had given no symptoms and did not interfere with mastication. Examination revealed a fusiform tumor mass at the angle of the jaw measuring approximately 6 by 4 cm. It extended backward, elevating the lobe of the ear. It was thought to be fluctuant and was freely movable in the subcutaneous tissue. No other significant findings were present. Roentgen examination of the parotid region showed no evidence of calcification or of a calculus.

Operation (April 24, 1928, by Dr. W. Barclay Parsons, Jr.).—With the patient under ethylene anesthesia, a curved incision was made and carried down to the wall of the cyst which was well encapsulated, lying in the substance of the parotid, but not apparently associated with the duct system. The cyst ruptured, with an escape of creamy material, allowing it to be enucleated with ease. An iodoform gauze drain was inserted.

Course.—The drain was slowly withdrawn, drainage being slight, and in one week the wound was completely healed. Three years later there was no evidence of reappearance.

PATHOLOGIC EXAMINATION

At operation it was noted that both of these tumors were within the substance of the lower pole of the parotid gland, but were distinctly encapsulated and separated from the salivary tissue.

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3. v. Schulte. H. W.: Studies in Cancer and Allied Subjects: II. The Development of the Human Salivary Glands, New York, Columbia University Press, 1913, vol. 4.

Macroscopic Examination.—The tumor from the first case was a rather firm, lobulated mass measuring 4 by 3.5 by 3 cm. Externally it was covered with a smooth capsule to which no appreciable parotid tissue was adherent. Cross-section through the central part of the tumor (fig. 1) showed irregular wide trabeculae of soft grayish tissue separated by masses of yellowish material. This has been
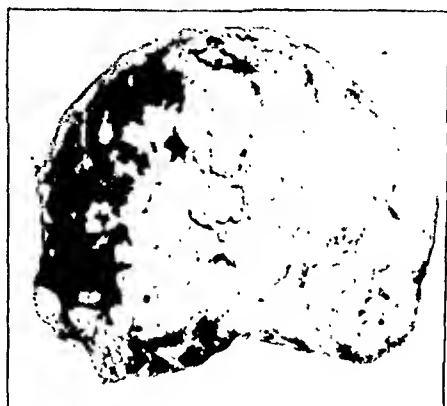
Fig. 1 (case 1).—Cross-section through the mass removed.

Fig. 2 (case 2).—The cystic mass cut open to show the papillary lining.

removed in some places, showing narrow clefts, but no large cystic acreas were present.

In the second case the specimen was distinctly a cystic structure measuring 3 cm. in diameter. The capsule was smooth, and on cut section the wall consisted of rather firm white tissue on the inner surface of which were small rounded elevations varying from 1 to 2 mm. in diameter (fig. 2).

Microscopic Examination.—In case 1, the tumor was composed of irregular masses of lymphoid tissue covered with epithelial cells. These were so arranged

Summary of Previously Reported Cases

Observer	Sex	Age	Location of Tumor	Pathology	Interpretation
Hildebrant: Arch. f. klin. Chir. 49:167, 1898	M	41	Left angle of jaw in parotid region	Flattened and ciliated epithelium covering lymphoid tissue showing germinal centers	Mentioned in report of 20 cysts and fistulas of the neck; all considered of branchiogenic origin
Sultan: Deutsche Ztschr. f. Chir. 48:118, 1898	M	44	Extending from left ear to masseter muscle	Stratified ciliated or columnar epithelium forming projections in lymphoid tissue	Mentioned in report of 22 cysts of parotid
Moresthi: Bull. Soc. anat. de Paris 4:709, 1902	F	23	Right posterior parotid region elevating ear	Stratified squamous epithelium; deeper cells polyhedral	Not similar to parotid glandular epithelium but derived from embryonal buccal ectoderm
Levéine: Rev. de chir. 37:1, 1908	F / M	40 / 50	Right parotid region	Adenoma of stratified and ciliated epithelium	Similar to embryonic tonsil; derived from pharyngeal ectoderm in region of third or fourth branchial pouch
Albrecht and Artz: Frankfurt. Ztschr. f. Path. 4:47, 1910	M / F	64 / 12	Left parotid / Right parotid	Both cystadenomas consisting of lymphoid tissue with follicles lined by high columnar nonciliated epithelium	(1) Changes in endothelium of lymph glands; (2) heterogenic epithelium derived from pharynx included in lymph gland; (3) from anlage of salivary duct epithelium
Glass; Frankfurt. Ztschr. f. Path. 9:335, 1912	M	65	Left angle of jaw	High cylindric epithelium containing eosinophilic granules resting on lymphoid tissue	Included epithelium in lymphoid tissue as cervical sinus closes
Delangiade, Peyron and Roushacroix: Bull. Assoc. franç. p. l'étude du cancer 7:350, 1914	F	33	Left parotid lower pole	Cylindric epithelium covering lymphoid tissue containing masses of concentric squamous epithelial cells	Similar to Hassall's corpuscles and possibly derived from thymus
Menetrier, Peyron and Surmont: Bull. Assoc. franç. p. l'étude du cancer 12:205, 1923	M	50	Parotid	Single or double layer of high columnar epithelium in some places ciliated. These rest on lymphoid tissue containing follicles	Parabranchial cyst not derived from branchial cleft; possibility of embryonal rest of undifferentiated salivary structures (Neisse: Anat. Hefte 10:287, 1898)
Mazza and Cassinelli: Rev. Assoc. méd. argent. 35:317, 1923	M	36	Left parotid	Ciliated columnar epithelium with lymphoid tissue	Branchiogenic cystadenoma similar to those of Albrecht and Artz
Ribi: Zentralbl. f. allg. Path. u. path. Anat. 35:310, 1924-1925	M	47	Right parotid	High cylindric epithelium in lymphoid tissue	Cellular incision by lymphoid tissue within the parotid gland as it develops
Askinazy, quoted by Sternburg in Henke and Lubarsch: Handb. d. spez. path. Anat. u. Histol., Berlin, Springer, 1926, pt. 1, vol. 1, p. 331; also by Lang, ibid., 1929, pt. 5, vol. 2, p. 127	M	51	Left parotid	Stratified cuboidal epithelium included in lymphoid tissue showing follicles	Reported in Lubarsch's textbook; some previous theories mentioned
Houdard and Hufnagel: Bull. Assoc. franç. p. l'étude du cancer 16:377, 1927	M	58	Parotid	Cystic tumor lined by high cylindric epithelium with lymphoid tissue showing germinal centers	Some previous theories reviewed
Spitzangel: Zentralbl. f. allg. Path. u. path. Anat. 46:282, 1929	M / M	65 / 45	Left parotid / Lower pole of left parotid	High cylindric epithelium resting on lymphoid tissue	Similar to that of Albrecht and Artz
Warthin: J. Cancer Research 13:116, 1929	M	60	Left parotid	Ciliated stratified columnar epithelium resting on lymphoid tissue	Similar to polyps of eustachian tube and represent developmental disturbance of eustachian tube anlage
Cunningham: Ann. Surg. 90:111, 1929	M	16	Right parotid	Stratified cylindric epithelium resting on lymphoid tissue	Branchiogenic origin
Hunford: Ann. Surg. 94:461, 1931	M	61	Lower pole of left parotid	Stratified cylindric epithelium resting on lymphoid tissue	Branchiogenic origin

Fig. 5 (case 2).—Photomicrograph showing that the papillary projections pictured in figure 2 are made up of lymphoid tissue clothed with epithelium.

Fig. 6 (case 2).—Detail photomicrograph showing the stratified cylindric epithelial lining resting on lymphoid tissue.

each author's interpretation of the origin of the cyst. Every writer recognized that neither the epithelial lining nor the lymphoid tissue was characteristic of the adult parotid and supposed that it must have come from some developmental aberration.

The earliest writer, Hildebrant,[4] mentioned his case in connection with the report of a group of branchial cysts of the neck and apparently thought it had the same origin. Morestin,[5] in 1902, suggested that these cysts must have been derived from evaginations of the embryonal buccal ectoderm within the parotid gland as it developed, although he did not support it with convincing embryologic and phylogenetic evidence. As will be shown later, this is the probable derivation, but Morestin was unfamiliar with the mechanism of their formation. The similarity of the epithelium to that of the pharynx and its close association with lymphoid tissue led Lecène[6] to suppose that the growth represented the development of an ectopic tonsil, and he traced its elements to an inclusion of a portion of the pharyngeal ectoderm in the region of the third or fourth branchial pouch. Glass[7] supposed the inclusion of a few pharyngeal ectodermal cells as the cervical sinus closes. Delanglade, Peyron and Rouslacroix[8] found a somewhat similar growth in the carotid region and reported it at the same time as their parotid cyst. They saw some concentrically arranged cells resembling Hassall's corpuscles, and they supposed a separation of a portion of the thymic anlage. Menetrier, Peyron and Surmont[9] studied Neisse's[10] drawings of the embryonal parotid tissue which show lymphoid tissue and epithelium resembling that found in the cysts. They therefore suggested that these tumors might be remnants of undifferentiated salivary structures which did not fuse with the duct system of the parotid but grew later as segregated tumors.

Warthin[11] studied a case in which the tumor was lined with ciliated epithelium. He noted a resemblance to some of the polyps of the eustachian tube and concluded that these parotid cysts might be derivatives of the first branchial pouch and cleft. He does not tell how this epithelium could be enclosed within the parotid. The other hypotheses

4. Hildebrant, O.: Arch. f. klin. Chir. **49**:167, 1898.

5. Morestin: Bull. Soc. anat. de Paris **4**:709, 1902.

6. Lecène, P.: Rév. de chir. **37**:1, 1908.

7. Glass, E.: Frankfurt. Ztschr. f. Path. **9**:335, 1912.

8. Delanglade; Peyron, and Rouslacroix: Bull. Assoc. franç. p. l'étude du cancer **7**:370, 1914.

9. Menetrier, P.; Peyron, A., and Surmont, J.: Bull. Assoc. franç. p. l'étude du cancer **12**:205, 1923.

10. Neisse, R.: Ueber den Einschluss von Parotsläppchen in Lymphknoten, Anat. Hefte **10**:287, 1898.

11. Warthin, A. S.: J. Cancer Research **13**:116, 1929.

included in the list do not seem to us to have sufficient credibility to warrant serious discussion.

All of these writers, then, believe that these cystic growths are derivatives of either the branchial pouch or the cleft epithelium, of the buccal or pharyngeal ectoderm other than that from which the parotid is developed or from segregated cells of the parotid anlage itself.

A brief review of the development and metamorphosis of the branchial system will make it clear that there is no embryologic basis for supposing that parotid cysts could represent developments from its remnants. In early embryonic life there are four external branchial arches separated by depressions or clefts externally and by pouches internally.[12] The clefts and the pouches are not continuous but are
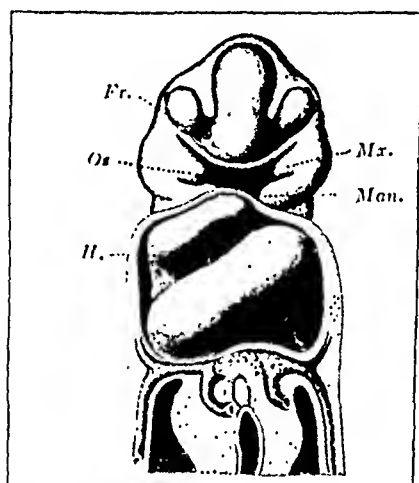
Fig. 7.—Ventral view of the anterior portion of an embryo of 2.15 mm., from a reconstruction (His). *Fr.* indicate frontal process; *H.,* heart; *Mx.,* maxillary process; *Man.,* mandibular process; *Os,* oral sinus. (Figures 7 and 8 are from Keibel and Mall: Human Embryology, Philadelphia, J. B. Lippincott Company.)

separated by a thin membrane covered by ectoderm on the outer surface and by entoderm on the inner surface. The first and second arches develop out of proportion to the third and fourth which they overlap, producing a deep depression called the cervical sinus.[13] It is supposed that a majority at least of the branchial cysts and fistulas in the neck develop from this structure.[14] These develop below the second or

12. Bailey and Miller: Textbook of Human Embryology, ed. 2, New York, William Wood & Company, 1911.

13. Semken, G. H.: Embryology of Branchiogenetic Cysts and Fistulae, in Nelson Loose-Leaf Living Surgery, New York, T. Nelson & Sons, 1927, vol. 2, p. 783.

14. Wood, F. C.: Branchiogenetic and Other Congenital Cysts, in Nelson Loose-Leaf Living Surgery, New York, T. Nelson & Sons. 1927, vol. 2, p. 113. Keith, A.: Congenital Malformations of Palate, Face and Neck, Brit. M. J. 2:438, 1909.

hyoid arch.[15] The first pouch and cleft form the eustachian tube and the external auditory canal and are separated by the membrana tympani. Since the parotid gland does not come into intimate relationship with any of these structures, it is difficult to understand how portions of them can be included within its substance. For this reason we have rejected the branchial hypotheses.

In order to discuss the possibilities of the remaining hypotheses that have to do with the segregation of some cells of the parotid anlage or of the oral ectoderm, the embryology of this region must be described. The first branchial arch divides into upper and lower portions.[16] The upper or maxillary portion is divided by the two nasal pits into a
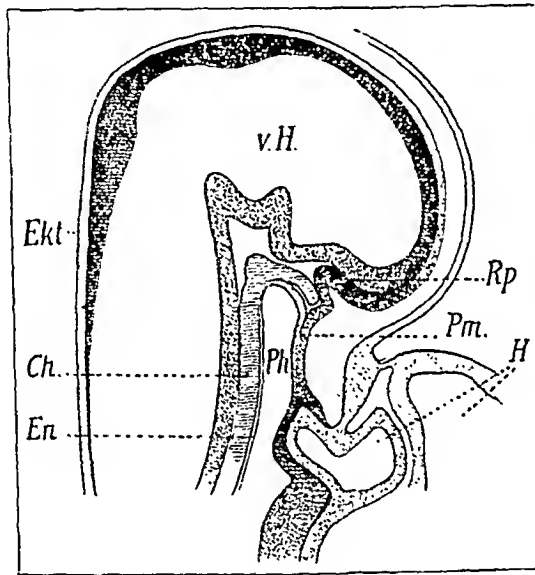
Fig. 8.—Median longitudinal section of a rabbit embryo. *Ch.* indicates chorda; *Ekt.*, ectoderm; *En.*, endoderm; *H.*, heart; *Rp.*, Rathke's pouch; *Ph.*, pharynx; *Pm.*, pharyngeal membrane; *v.H.*, forebrain.

medial portion giving rise to the lips and a lateral portion from which the cheek is formed. The lower portion of the first branchial arch forms the mandible. The primitive oral sinus is pentagonal, having for its boundaries laterally the maxilla and mandible and superiorly the frontal process of the brain, while inferiorly it is separated from the pericardium by a thin membrane (fig. 7). In a 2 mm. embryo the floor of the oral sinus is formed by a membrane which separates it from the pharynx. This is lined on the oral side by ectoderm and on the pharyngeal side

15. Carp, L., and Stout, A. P.: Branchial Anomalies and Neoplasms, Ann. Surg. **81**:186, 1928.

16. McMurrich, J. P., in Keibel and Mall: Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 7, p. 335.

by entoderm (fig. 8). In the 2.5 mm. stage this membrane has disappeared and the oral sinus and pharyngeal cavity are continuous, leaving as a remnant only a transverse ridge immediately posterior to Rathke's pouch. The lateral and superior lining of the buccal cavity therefore is derived from ectoderm. The floor of the mouth and the tongue are derived from three sources: (1) the tuberculum impar anteriorly, formed by the fusion of the mandibles; (2) the lateral portions, formed from the fusion of the second branchial arches, and (3) the base or copula, formed from the medial expansions of the third and fourth branchial arches.

In the lateral recess of the oral cavity there is a sulcus which extends from the angulus oris to the opening of the first pharyngeal pouch. Schulte [a] called this the buccal sulcus. In embryos of 8 mm. there is a slight thickening of the epithelium along the fundus of this sulcus near the angulus oris (fig. 9 A). This is the anlage of the parotid

A   B
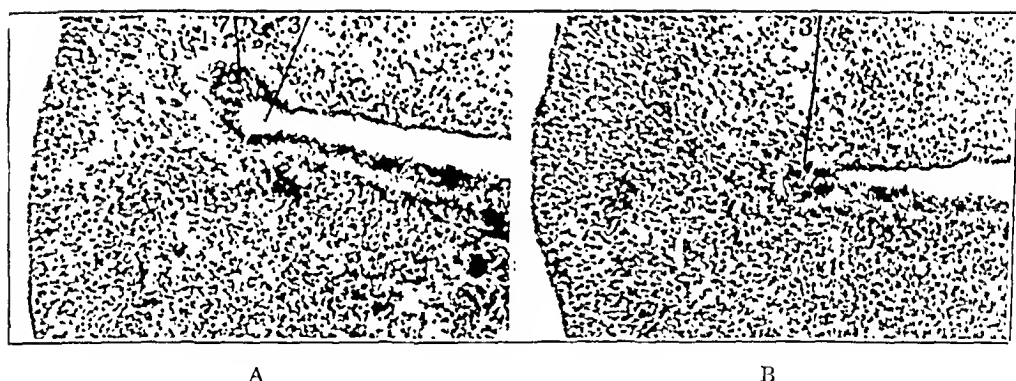
Fig. 9.—A, transverse frontal section of the buccal sulcus near the angulus oris of a 20 mm. human embryo. The first evidence of beginning parotid development is a thickening of the epithelium of the buccal sulcus (7). B, transverse section of the buccal sulcus more caudad than A, showing the epithelial thickening (3) which gives rise to the orbital inclusion. (Figures 9 to 12 are from Schulte: Studies in Cancer and Allied Subjects: II. The Development of the Human Salivary Glands, New York, Columbia University Press, 1913, vol. 4.)

gland. Further thickening occurs until a flange of epithelium develops which grows backward (fig. 10, 2) through the mesenchyme of the cheek crossing the internal surface of the masseter and pterygoid muscles until it reaches the neighborhood of the external ear. This flange becomes canalized, and sprouts develop from it. By a continuation of this process of sprouting the embryonal gland eventually comes to assume its adult form.

In the past there have been described what seemed to be accessory parotid anlages, and those who observed them supposed that they were derived from the parotid duct. In the series of observations made by

Weishaupt,[17] the hypothesis was advanced that these structures became separated from the parotid duct system and remained vestigial. If this observation is correct there would be strong grounds for supposing that such vestigial segregated closed tubular structures might be the origin of cysts. For this reason we shall review these observations in some detail.

In 1885, Chievitz [18] reported that he found in a 9 to 10 week human embryo a small solid branch of cells given off superiorly from the
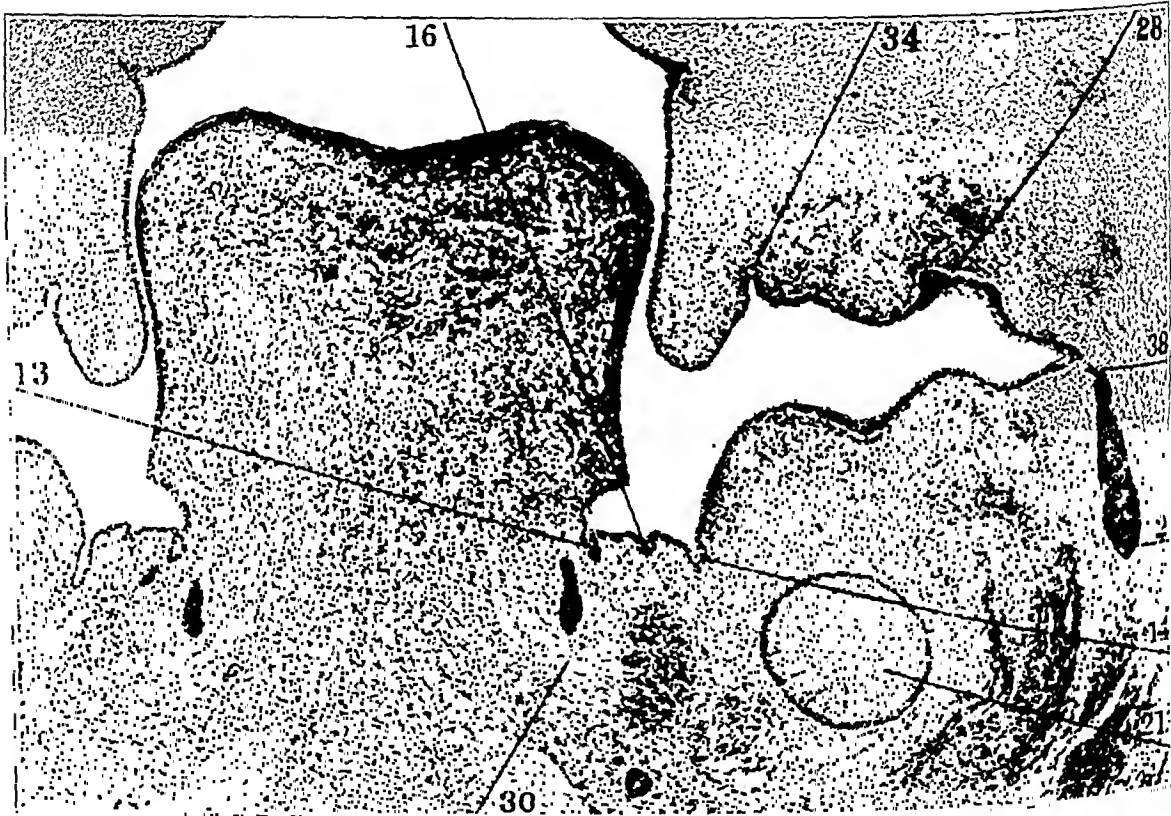
Fig. 10.—Transverse section of a 20 mm. human embryo showing the separation of the parotid anlage from the buccal sulcus; 2, parotid anlage; 13, postglandular flange; 14, alveolar sulcus; 16, intermediate sulcus; 21, Meckel's cartilage; 28, superior dental anlage; 30, lingual nerve; 34, ectopalatine sulcus; 38, orbito-parotid.

parotid duct as it passed along the masseter muscle. In a 12 week embryo he found a similar structure which arose from the parotid duct and had a course about 1 mm. long from the masseter to the pterygoid

17. Weishaupt, Elizabeth: Ein rudimentärer Seitengang des Ductus Parotideus. Arch. f. Anat. u. Entwcklngsgesch., 1911, p. 11.

18. Chievitz, J. H.: Beiträge zur Entwickelungsgeschichte der Speicheldrüsen, Arch. f. Anat. u. Entwcklngsgesch., 1885, p. 401.

where it ended blindly. It was lined with epithelial cells with oblong nuclei arranged about a lumen. Chievitz considered this structure an accessory parotid.

In 1911, Elizabeth Weishaupt [17] described an embryonic structure that she found on both sides in twenty of twenty-four human embryos and on one side in one of the other four. This was a blind tube, not connected with the ductus parotidis, which lay near the duct between the mucous membrane of the buccal sulcus and the anterior border of the masseter muscle. It was smaller than the normal ductus parotidis, lined with epithelium and surrounded by the mesenchymal tissue. In one
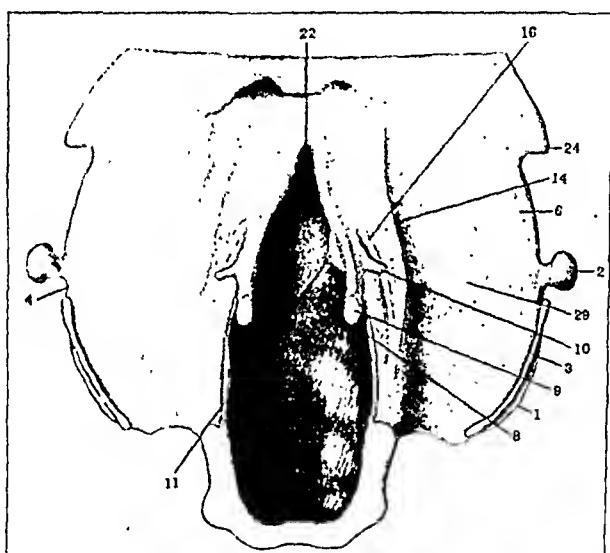
Fig. 11.—Reconstruction of the oral epithelium of a 20 mm. human embryo; ventral view showing the relation of the orbital inclusion to the parotid gland anlage: *1*, buccal sulcus; *2*, parotid anlage; *3*, orbital inclusion; *4*, orbitoparotid interval; *6*, proparotid ridge; *8*, lingual sulcus; *9*, submaxillary anlage; *10*, greater sublingual gland; *11*, anlage of apical gland; *14*, alveolar sulcus; *16*, intermediate sulcus; *22*, frenulum; *24*, angulus oris; *29*, inferior dental anlage.

24 mm. human embryo it was cystic at both ends, the lumens being lined with flattened cells which in some places were forced in toward the center of the lumen. This structure she called the "ramus mandibularis" of the parotid duct. She expressed the belief that it is vestigial in man and is not developed into any adult structure. In mammals she supposed that it represented the anlage of the dorsal and ventral buccal glands. Weishaupt and McMurrich,[16] who also observed this structure in human embryos of 9 weeks and earlier, remarked that

its significance was unknown in human beings, but that since it was a tube with blind ends it might give rise to cysts.

It is obvious that Chievitz and Weishaupt described the same structure, and that its vestigial tubular character favors the development of cysts. Were they correct in their hypothesis that it was derived from the anlage of the parotid, then we should agree with Menetrier, Peyron and Surmont [9] that the cysts came from segregated embryonal parotid gland.
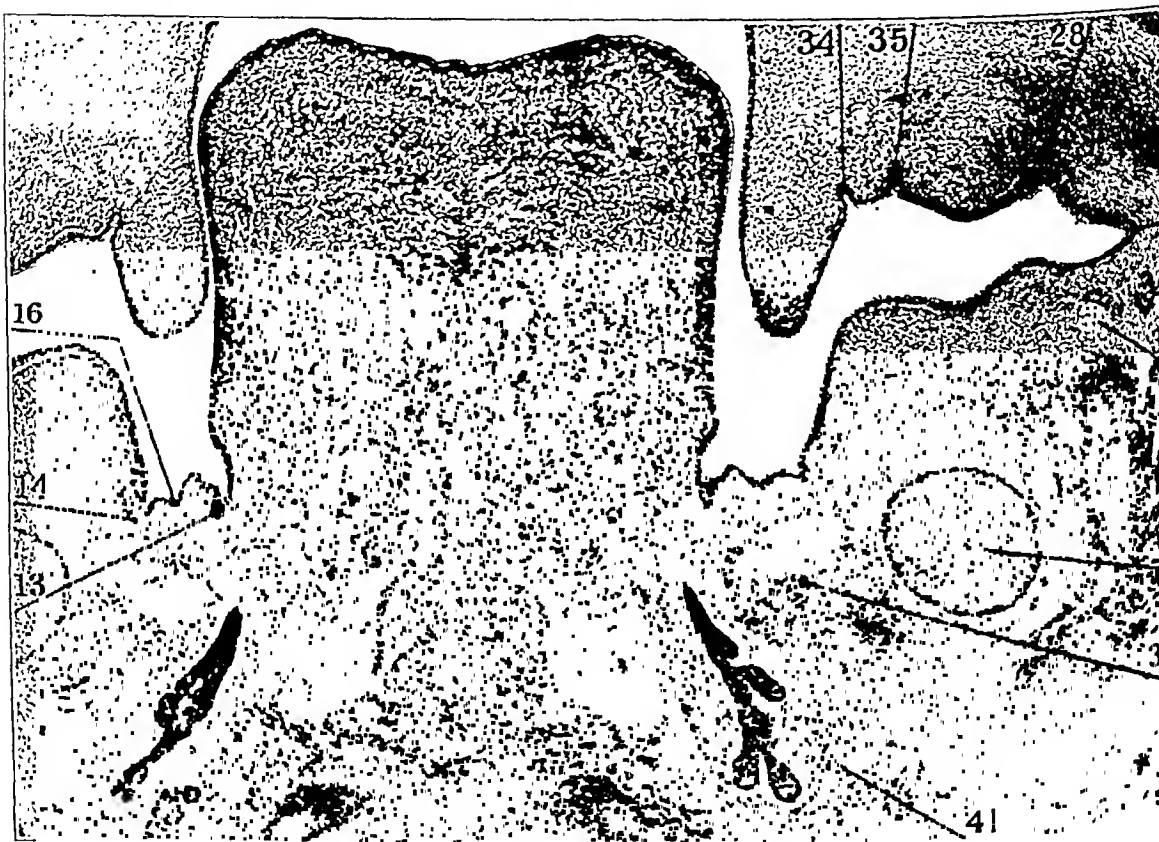
Fig. 12.—Transverse section of a 20 mm. human embryo through the buccal sulcus, more caudad than in figure 10, showing the orbital inclusion separated from the sulcus: *1,* buccal sulcus; *3,* orbital inclusion; *33,* buccal nerve.

However, the investigations of Schulte,[3] Huntington[19] and Carmalt[20] into the development and comparative anatomy of the whole salivary

19. Huntington, George S.: Studies in Cancer and Allied Subjects: III. The Anatomy of the Salivary Glands in the Lower Primates, New York, Columbia University Press, 1913.

20. Carmalt, Churchill: Studies in Cancer and Allied Subjects: V. The Anatomy of the Salivary Glands in the Carnivora, New York, Columbia University Press, 1913.

system, published in 1913, showed conclusively that the structure described by Chievitz and Weishaupt has a different origin and is not part of the parotid anlage. Schulte [3] showed that in human embryos of from 9 to 10 mm. there occurs a continuous thickening along the fundus of the buccal sulcus posterior to the anlage of the parotid and separated from it (fig. 11, 3). Out of this continuous anlage, a cylinder of cells is formed by a process of folding and constriction (fig. 9 B). Ultimately this group of cells is widely displaced laterad from the oral ectoderm (fig. 12, 3) and comes to lie in close contact with the ental surface of the muscles of mastication. This structure Schulte calls the orbital inclusion and identifies it with those described by Chievitz and Weishaupt. He explains Chievitz' observation of a communication with the parotid duct near its outlet in the buccal sulcus by saying that sometimes there is no orbitoparotid interval between the parotid anlage and the orbital inclusion, and in such case a development from the orbitoparotid (fig. 11, 4) might be attached to the parotid duct. As the parotid gland increases in size it approaches nearer and nearer to the orbital inclusion until, finally, in embryos of 12 weeks they lie in contact with one another. The subsequent fate of the orbital inclusion in man has never been investigated, but in the cat, dog and some other carnivora it forms the orbital glands. These are salivary glands which are embedded in the infra-orbital fat. Their ducts, according to Carmalt,[20] open on a low stomal ridge opposite and behind the upper molars.[21]

In man, therefore, the orbital inclusion is a vestigial closed tubular structure, lined with ectodermal epithelium which lies in contact with the lower portion of the parotid gland. It is well known that closed tubular vestiges in other parts of the body may form cysts in adult life. Weishaupt [17] recorded microscopic cystic dilatation of one of the orbital inclusions that she studied. For these reasons it seems fair to assume that the probable origin of these lympho-epithelial cysts of the matured parotid is from a dilatation and proliferation of the orbital inclusion.

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21. Carmalt (footnote 20) described a series of orbital glands in man which are situated in series with the superior alveobuccal glands but behind the opening of the parotid duct. These are not developed from the parotid duct but probably from the orbitoparotid interval. Other authors have called them malar glands.

PRESERVED FASCIA IN HERNIA REPAIR

WITH SPECIAL REFERENCE TO LARGE POSTOPERATIVE HERNIAS

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During the last decade there have been many innovations in the operations for the various types of hernia, as regards both the technic of the operations themselves and the materials used in the repair. My object in this paper is to discuss briefly, in general, the use of fascia strips, with especial reference to the preserved material, and then to discuss specifically the application of the method to one of the most difficult problems in hernia, namely, large postoperative hernias.

Gallie and LeMesurier,[1] in recent years, have extensively employed autogenous fascia lata in the repair of hernial defects. They have largely used strips of fascia lata, either as an ordinary suture material to approximate the edges of hernial defects, or, in gaps, the edges of which cannot be approximated, as a basketweave network to close the defects. They have shown experimentally that such transplants persist as living tissues and become incorporated into the tissues among which they are transplanted as an integral part of the organism. They constitute, therefore, not merely an additional suture material, but, in addition, perform all the functions of grafts. They form a most noteworthy contribution to the surgical armamentarium.

I[2] have shown that animal fascia preserved in alcohol may be used in exactly the same way as living fascia taken from the thigh of the patient that is being operated on (figs. 1 and 2). This avoids the necessity of performing an extra operation in order to get the material needed to repair the hernial defect. Briefly, the underlying principles in the use of alcohol-preserved animal fascia may be stated as follows: The collagen fibrils of the connective tissues are inert, intercellular substances, and have no life in the sense that living protoplasm has life. These fibrils are not altered chemically or physically by being preserved in alcohol. When implanted in a living organism among their fellows

1. Gallie, W. E., and LeMesurier, A. B.: The Transplantation of the Fibrous Tissues in the Repair of Anatomical Defects, Brit. J. Surg. **12**:289 (Oct.) 1924.

2. Koontz, A. R.: Experimental Results in the Use of Dead Fascia Grafts for Hernia Repair, Ann. Surg. **83**:523 (April) 1926.

of the same kind (after being thoroughly washed in salt solution), one would not then expect them to produce a foreign body reaction, induce phagocytosis or show a tendency to be absorbed. They are like the tissues among which they have been implanted, both chemically and physically, and it has been shown experimentally that living cells wander in among the inert fibers, new fibroblasts grow in between them, and in a short time the implanted material is incorporated with the tissues of the host as permanent living material. The reason that catgut

Fig. 1.—Repair of large ventral hernia in an animal with a piece of alcohol-preserved ox fascia lata; five months after operation.

and kangaroo tendons do not act in the same way is that the collagen fibrils of these materials are altered both chemically and physically in the process of their preparation. Various chemicals, such as chromic acid, are used, and they are also heated in the process of preparation. Besides, their strands are generally so twisted and hardened that it would be impossible for fibroblasts from the surrounding tissues to grow into them, even if there were no question of a complicating chemical and physical alteration of the fibrous framework.

Since the publication of my first work on dead fascia grafts, strips of alcohol-preserved fascia have come to be widely used in the repair of hernial defects. This material has been used in other operations, such as those of habitual dislocation of the shoulder, repair of the sphincter ani in cases of fecal incontinence, open reduction of fractures, etc. My experimental results and conclusions as to the fate of alcohol-preserved fascia have been confirmed experimentally by Rosenblatt and Meyers[3] of Detroit, McNealy and Lichtenstein[4] of Northwestern University, and Horsley[5] of Richmond. Also, Wolfsohn[6] has shown that strips of fascia preserved in a solution of 1 part formaldehyde and 100 parts of alcohol, after implantation in animals, retain their tensile strength for as long as twenty-one months, which was as long as obser-
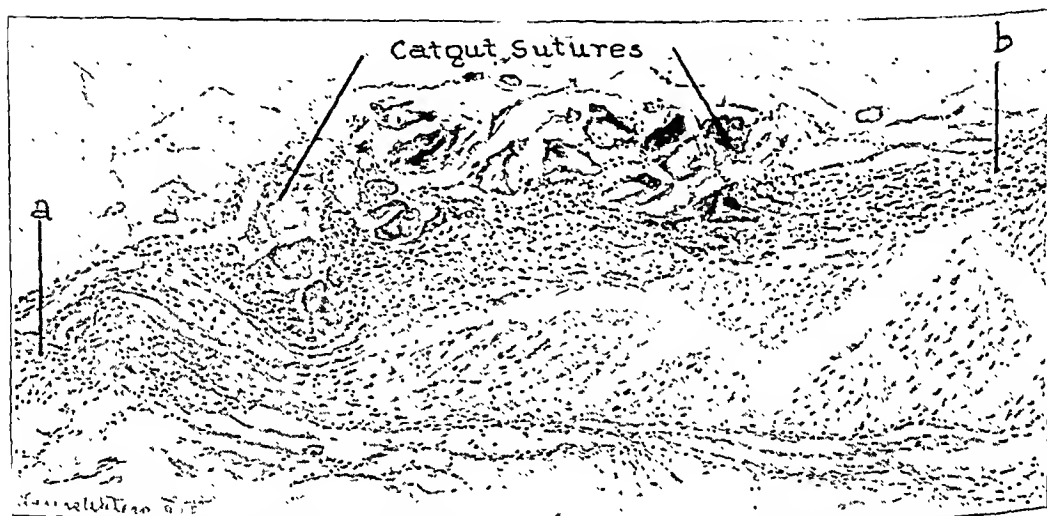
Fig. 2.—Microscopic drawing showing union of preserved and living fascia four months after operation: *a,* living fascia of host; *b,* dead graft.

vations were made. Besides, numerous other European investigators have confirmed the original work of Nageotte as to the fate of preserved tendons when implanted in animals. As the connective tissues of tendon and fascia are so nearly related, it is to be presumed that the behavior of these materials when implanted would be similar. Some workers

3. Rosenblatt, M. S., and Meyers, M.: Muscle-Fascia Suture with Preserved Fascia and Tendon, Surg., Gynec. & Obst. **47**:836 (Dec.) 1928.

4. McNealy, R. W., and Lichtenstein, M. E.: A Study of the Use of Fascial Grafts, Illinois M. J. **56**:140 (Aug.) 1929.

5. Horsley, G. W.: The Behavior of Alcohol-Preserved Fascia Lata of the Ox, Autogeneous Fascia and Chromicized Kangaroo Tendon in Dog and in Man, Ann. Surg. **94**: 410 (Sept.) 1931.

6. Wolfsohn, G.: Ueber die Verwendung von tierischen Fascienfäden, Arch. i. klin. Chir. **147**:479 (Oct. 15) 1927.

claim that when these tissues are implanted there is a substitution of fibers from the host for the implanted fibers. Others claim that the implanted fibers remain intact and function as a part of the host. This question is a matter of academic interest, but of no real practical importance. It matters little whether the implanted material functions as originally implanted, or by the use of fibers borrowed from the host. The point of practical interest is that the implant does function.

Horsley's article [*] contains some rather surprising conclusions. After reporting his experiments, which confirmed mine as to the fate in dogs of alcohol-preserved ox fascia lata, he stated that "from clinical experience the reactions of this alcohol-preserved fascia lata of the ox in man have been contrary to what would be expected from these experiments in dogs." This conclusion is based almost entirely on two human operative cases, one a pyloroplasty and the other a gastro-enterostomy, in which the abdominal wounds were closed in layers, catgut being used throughout, except in the anterior sheath of the rectus, which was closed with a continuous suture of alcohol-preserved ox fascia lata. Within ten days after operation both wounds broke open. It seems to me that Horsley's conclusions that alcohol-preserved fascia behaves differently in man and in the dog is based on insufficient evidence. I have discussed this in detail elsewhere.[7] I do not believe that fascia should be used in closing the wound after operations on the stomach, owing to the action of the digestive juices on the fascia.

The fact that myself [8] and many other surgeons have used alcohol-preserved ox fascia lata successfully in repairing difficult hernia shows that the material does remain intact in man for a considerable length of time, at least long enough to effect cures in cases in which other methods have failed. I have used the material in eighty-five operations for hernias of all sorts, many of which were difficult and were referred to me only because it was felt that they were hopeless as to cure, but that it would do no harm to try a fascial repair. In spite of the large number of difficult cases, I know of only three recurrences. I will cite only one case, which seems to me ample proof that preserved fascia persists in man just as it has been shown experimentally to persist in dogs. This case was that of a man, aged 70, who had been operated on five times before for a left inguinal hernia. Each time the hernia had recurred within a month or two after operation. The patient was referred to me by the surgeon who had operated on him the fifth time, and who felt that the hernia could not be cured by the usual methods.

7. Koontz, A. R.: Suture Material for Hernia Repair, with Special Reference to Preserved Fascia Strips, South. M. J. **25**:372 (April) 1932.

8. Koontz, A. R.: Dead (Preserved) Fascia Grafts for Hernia Repair: Clinical Results, J. A. M. A. **89**:1230 (Oct. 8) 1927; New Principles and Procedures in Hernia Repair, Texas State J. Med. **24**:259 (Aug.) 1928.

He had a scrotal hernia about the size of a cocoanut, which could not be reduced when he was examined at my office. At operation an enormous amount of dense scar tissue was encountered, but the different layers were dissected out as well as possible. The sac contained several loops of intestine which were adherent to its wall. The neck of the sac was 3 inches (7.6 cm.) in diameter. After the sac had been dissected free and excised, the peritoneal opening was closed with a running suture of fine black silk. The hernia was then repaired with alcohol-preserved ox fascia lata strips, making a basketweave according to the Gallie technic. It has now been more than five years since this patient was operated on, and there has not been the slightest evidence of a recurrence. Many other such examples could be cited.

A rather striking example of the efficacy of the material is found in the recent report of Stone [9] on the voluntary control of incontinent anal sphincters by the use of double loops of fascia lata encircling the anus and a portion of the gluteus muscles. Here the control is entirely dependent on the loops of fascia constricting the anus through voluntary contracture of the gluteus muscles. Stone has reported eleven cases in which this method was used, with nine good and two poor results. In four of the successful cases, strips of alcohol-preserved fascia were used. Naturally, if the fascia were absorbed soon after implantation, these patients would have lost anal control. The fact that the patients have now maintained anal control for two years or more after operation is positive proof that the fascia is still functioning. This is a striking clinical example of the usefulness of the material. It matters little whether the original strands of ox fascia are still present in these persons, or whether they have been replaced by fibers from the host. The functional result is the same.

LARGE POSTOPERATIVE HERNIAS

Small postoperative hernias often present one of the easiest problems in major surgery, and are usually easy to cure by any careful procedure that the surgeon may select. On the other hand, large postoperative hernias are extremely difficult to cure, and often present one of the most troublesome problems that the surgeon has to confront. Of course, the ideal way to treat a large postoperative hernia is to operate when it is small and the operation is easy. There is a much larger proportion of large hernias in this group than in any other group. Some postoperative hernias are large from the beginning, owing to a general breaking down of the operative incision. This type usually develops soon after operation, and may develop while the patient is

9. Stone, H. B.: Plastic Operation to Restore Voluntary Anal Control, J. A. M. A. **97**:1205 (Oct. 24) 1931.

still in bed. In another group, the hernia is small to begin with and may remain so for years. However, once it starts to enlarge the progress is fairly rapid, owing to the nonresisting nature of the soft parts surrounding the hernia. The muscles and fascia are often thinned out and weakened, and yield readily to the constant force of intra-abdominal pressure exerted against them. The large hernias generally cause rather severe symptoms, such as an uncomfortable sense of weakness in the abdominal wall, dragging down pain, digestive disturbances, constipation and inability to engage in any sort of strenuous work. Some of the hernias become so large as to incapacitate the patient completely. I recently operated on one so large that an abdominal support was no longer of much help, and about the only way the patient could lead an even moderately comfortable life was to sit around and hold his abdominal contents back with his hands. However, the presence of a postoperative hernia should not preclude the surgeon from thinking of a concomitant condition which might be responsible for the patient's symptoms, such as gastric or duodenal ulcer, colecystitis or colelithiasis and kidney or ureteral stone. Patients suffering with these conditions have been operated on for hernia, with a cure of the hernia, but, naturally, without relief of symptoms, when the symptoms were due to some other condition.

A good many large, postoperative hernias occur in obese persons. In fact, obesity is an important etiologic factor in their production. Before operating on such patients, rigid dietary measures should be introduced in an effort to reduce their weight. A great deal of the excess weight of obese persons is carried in the omentum, and a reduction of this omental fat not only makes the operation easier, but the chances of recurrence less.

OPERATIVE TECHNIC

As to the operation itself, an elliptic incision is made surrounding the old operative scar. The skin and scar within this incision are then excised. Care must be exercised in excising this tissue to prevent injury to the contents of the sac, as the sac is often adherent to the old scar, and if it is inadvertently opened some adherent viscus may be injured. After excising the scar, if the sac has not already been located, it is carefully searched for, and is usually found covered by little connective tissue. It is usually more convenient to open the sac, and, with one finger on the inside as a guide, to free it from the subcutaneous tissue by blunt dissection with a piece of gauze. However, if the sac is large and protruding viscera are apt to prove troublesome, it is better to free the sac before opening it. The sac should be freed down to its neck, and then the fascia carefully cleaned for 2 inches (5 cm.) in each direction from the hernial orifice. The sac is disposed of in the usual manner, after carefully freeing any adherent viscera that it may contain. Adherent omentum should be ligated and excised with the sac. Adherent bowel is easily injured, and, if necessary, islands

however, an ultimate cure is far more likely to be secured when these sutures are used. It is far better to have a cure with a sinus that persists for a few months leading down to a nonabsorbable suture, than to have a recurrence soon after operation following the use of catgut. This, of course, applies to massive hernias that are closed under considerable tension and that are difficult to cure no matter what procedure is used. I have had no trouble with persisting sinuses since I have been using the stab wound in the flank to drain off serum collections. Before this, when employing drainage in the operative wound, I had several cases in which there were sinuses which persisted for months, but which did not prevent an ultimate cure. These sinuses were probably due to the fact that linen was used in tying off the ends of the fascia strips. I think that linen or silk should always be used for this purpose, instead of catgut or kangaroo tendon, as one cannot be sure how long the latter materials will resist absorption.
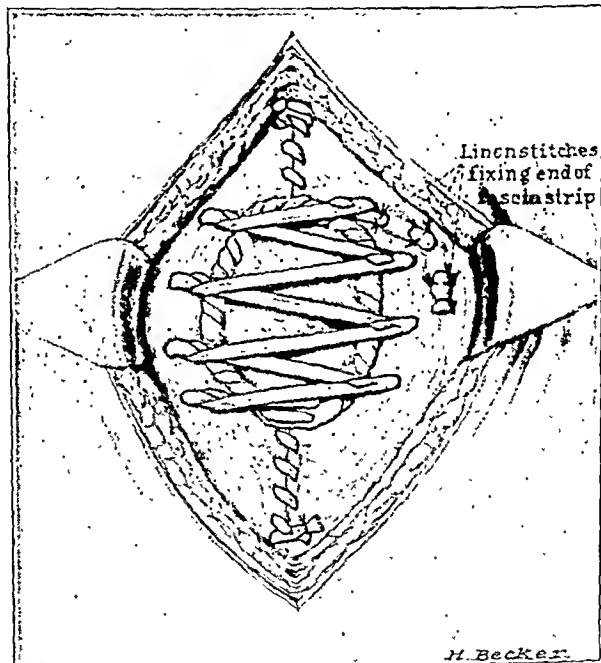
Fig. 4. — Repair of large postoperative hernia, showing the reenforcement lace-work of preserved ox fascia strips overlaying the free graft of the same material. The terminal end of the fascia strip is sutured in place with linen, instead of the end being split and tied into a knot as Gallie recommended.

It is important that the ends of the fascia strips remain tied off for a considerable length of time, as in most cases they are submitted to considerable stress. In one case I used no. 1 chromic catgut to tie off the ends of the fascia strips used in the repair of a massive postoperative hernia in an obese person. Following operation there was a large, subcutaneous collection of serum, and two days after operation the patient felt the wound give way in its deeper part. The skin did not break open, but the separated edges of the deep fascia could readily be palpated. It is safe to assume that the chromic catgut became softened by the collection of serum, and, being under considerable stress, some of the knots became untied and released the fascial ends, thus allowing the wounds to separate. Two years later this hernia, which was then even larger than at the time of the

first operation, was repaired in exactly the same manner, except that the ends of the fascia strips were tied with linen instead of catgut. Again there was a huge collection of serum, which drained for more than a week through a stab wound in the flank. Postoperative pneumonia also developed, and the patient coughed a great deal. In spite of all this, there has been no recurrence, although the second operation was done six months ago.

The prospect of cure in these cases depends on the size of the hernia, its location and the strength of the structures surrounding the defect. A hernia just under the costal margin is difficult to repair because of the rigidity of adjacent structures. A hernia appearing just above the pubic bones comes in the same category. I once repaired a massive hernia in this region by means of preserved fascia strips, but when the operation was over I was not satisfied that the defect was firmly closed at the lower border, which was formed by the unyielding pubic bone. A small recurrence soon appeared at this point. I am convinced that the proper procedure in this case would have been to drill holes in the pubic bone and to insure a cure by running the fascia strips through the holes in order to bring the abdominal fascia into snug apposition with the bone, thus effecting a secure closure of the lower border of the defect. An attempt had been made to run the fascia strips under the periosteum of the bone, but apparently the bite was not strong enough to be effective.

CONCLUSIONS

No one can see many large postoperative hernias and note the distressing symptoms and disabling effects that they produce without being impressed with the responsibility of the physician in seeking to avoid this almost entirely preventable condition. Small postoperative hernias are easy to cure, and large ones may be difficult or impossible to cure. This should always be carefully pointed out to the patient, and the natural tendency to put off the operation should be firmly discouraged.

STAB WOUND OF THE HEART

A REPORT OF TWO CASES

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It is with some hesitancy that I report these two cases of stab wound of the heart, with recovery in one after a cardiorrhaphy, as I realize that the operation of suturing the heart muscle in wounds of that organ has been performed many times during the last thirty years, with recovery of the patient in from 50 to 60 per cent of the cases, and that, in the last few years, much valuable work on the surgical treatment of the heart has been published. However, it must be recognized that all has not been learned concerning this condition, for the chance of seeing such cases does not come to every surgeon, and few see more than one, and as each case may present some particular condition not found in the others, there is reason for publishing its history so that a large number of cases may be collected for study. Unfortunately, most of the reported cases are the successful ones, while those in which the patients died are forgotten, though in many instances the findings, if reported, might have been of the greatest value, and a more exact rate of mortality would have been obtained. Therefore I am reporting two cases that contain facts of interest.

My first experience with a patient suffering from a wound of the heart occurred in 1915. at which time I operated on a man with a penetrating wound of the chest which involved the heart.

REPORT OF CASES

CASE 1.—*History.*—A man, aged 28, an Italian, was admitted to the prison ward at Bellevue Hospital on the morning of Sept. 22, 1915, having shortly before admission been stabbed in the chest with a large carving knife.

Examination.—The man was in an extreme state of shock and unconsciousness; respirations were rapid and labored. Over the edge and parallel to the left costal margin was an incised wound measuring about 1½ inches (3.5 cm.) in length, the mesial end of which was about ½ inch (1.3 cm.) from the midline. With every inspiratory movement of the chest there was a gush of dark blood from the wound.

Operation.—Since the operating room was prepared, the patient was immediately taken there, and, without anesthesia, a skin incision was made just lateral to the left border of the sternum at the level of the second costal cartilage and carried down to the fourth cartilage and thence obliquely outward. The skin flap so

formed was raised. The fourth and fifth costal cartilages were resected and the
sixth and seventh divided. On entering the anterior mediastinum, a large amount
of blood was evacuated and a wound was found which penetrated the wall of the
chest immediately above the attachment of the diaphragm to the costal border.
This was "sucking," and was found to communicate with the left pleural cavity,
and to lead also into the pericardial sac. When the pericardium was opened, a
large number of blood clots were found, and a wound 1 inch (2.5 cm.) in length
was discovered on the anterior surface of the heart, along its lower border. From
this a large quantity of blood spurted with each movement of the heart. An
attempt was made to suture the wound, the heart being steadied by means of
Allis clamps. However, before the suture was completed, the patient died. The
estimated period of time from the infliction of the wound to the time of death was
between three quarters of an hour and one hour.

Autopsy.—Autopsy was performed on September 22 by Dr. Otto Schultze,
medical assistant to the District Attorney of New York County. The important
facts discovered by this examination follow : The body was that of a young man,
5 feet 2¼ inches (158.1 cm.) in height, weighing 130 pounds (59 Kg.), with good
muscular development. Rigor mortis was extremely marked. The mucous mem-
branes of the lips were pale. The stab wound was found to be 1½ inches in
length, situated on the left side of the anterior surface of the thorax, the upper
end of the wound being ⅜ inch (1.2 cm.) to the left of the median line and the
lower end ¾ inch (1.9 cm.) to the left of the median line, therefore being slightly
oblique and situated over the cartilaginous margin of the thoracic wall. The wound
passed through the seventh and eighth costal cartilages above the diaphragm and
then through the pericardium, and also opened the left pleural cavity. The wound
through the anterior wall of the pericardial sac extended from the diaphragm
upward, and corresponded to the external wound, measuring 1¾ inches in length.
The sutured wound of the ventricle was 1 inch in length and extended over the
anterior surface of the right ventricle to the margin of the right ventricle at the
junction with its diaphragmatic surface, corresponding in situation exactly with
the stab wound described in the skin. There were two sutured wounds on the
external surface of the left ventricle; one extended from the apex upward for a
distance of ½ inch, the other wound was ¾ inch above and was identified as being
produced by a clamp used to raise the heart at the time of operation. When the
heart was opened, a wound through the interventricular septum was found, which
measured 1 inch in length and corresponded in position with the external wound
in the skin and with the wound in the wall of the right ventricle of the heart. The
sutured wounds described on the external surface of the left ventricle showed no
corresponding wound in the endocardium, so the knife passed through the wall of
the right ventricle and interventricular septum. The thickness of the thoracic wall,
including the costal cartilage, muscles and skin, was about 1 inch. The distance
from the wound in the interventricular septum to the wound in the wall of the
right ventricle was 2½ inches, allowing 1 inch for the thickness of the wall of the
chest, so that the whole depth of the wound, from the skin to the interventricular
septum, was 3½ inches.

The left lung was partly collapsed. Its pleural sac contained about 1 quart of
bloody fluid and a few drachms of blood clot. The right pleural sac was obliter-
ated by old adhesions.

All the organs showed signs of acute anemia.

Comment.—In case 1 it should be realized from the observations at
autopsy that the extent of the injury was not of a type in which a

successful outcome could be expected, and it seems difficult to explain how the patient lived as long as he did, as death was apparently due to acute hemorrhage, cardiac tamponade playing little if any part in the fatal outcome. A break in the operative technic was made by grasping the surface of the heart with Allis clamps, as these tore the musculature.

However, the experience gained in this case stimulated further study in the hope that at some future date a similar injury might be seen. In the spring of 1927, the occasion arose.

CASE 2.—*History.*—A Negro, aged 23, was admitted to Lincoln Hospital at 11 a. m. on June 2, 1927, having just been stabbed in the chest with a pair of scissors.

Examination.—The patient was in deep shock, and it was difficult to arouse him; his skin was cold and clammy, his pulse was imperceptible at the wrist, and his heart sounds could not be heard. At a point level with and 1 inch to the right of the left nipple there was an incised wound measuring ¾ inch in length. The cardiac dulness was said to be enlarged to the left and downward. The pericardial sac was aspirated, and about 100 cc. of blood withdrawn; immediately, following the aspiration, the patient's condition improved, and he apparently was more comfortable. At this time his temperature was 100 F., the pulse rate, 94 and the respiratory rate, 30. A roentgenogram, obtained with a portable apparatus, showed a general clouding of the lower left side of the chest.

I first saw the patient at 3 p. m., four hours following the injury. At this time the pulse was rapid but of fair quality. The apex beat was seen in the fifth interspace and the nipple line; the cardiac dulness apparently was not enlarged, and the heart sounds were normal. The blood pressure was 110 systolic and 76 diastolic. At 7:45 p. m., approximately nine hours after the injury, the patient's pulse became rapid and weak and the respirations dyspneic. The apex beat had disappeared, and the cardiac dulness was found to be enlarged to the left. The heart sounds were distant. The patient was operated on at 8:15 p. m., ten hours following the injury. Ether anesthesia was used.

Operation.—A vertical incision was made over the midline of the sternum at the level of the second rib and carried down to the level of the costal cartilage of the fifth rib. A second incision, starting at the latter point, was made for 3 inches (7.6 cm.) over the fifth costal cartilage and rib. The triangular flap thus formed was raised from the ribs and intercostal muscles. The perichondrium over the fourth and fifth ribs was separated, and the cartilages of the ribs were divided close to the sternum. The cartilages were then broken at their junction to the ribs. As soon as the cartilages of the fifth rib were separated from the underlying tissues, there was a gush of bright red blood, which was found to be emerging from a wound about 1 inch in length in the pericardial sac. The internal mammary artery was doubly ligated and divided. The third costal cartilage was separated at its junction with the sternum, and retracted upward and outward. The fibers of the triangular muscles were separated, and the pericardial sac exposed. The latter was opened by a vertical incision along the left border of the sternum for about 3 inches. In addition to the bright red blood that had already been evacuated, a large number of red and "chicken fat" clots were found in the pericardial sac. Two transverse wounds on the anterior surface of the left ventricle were found. A stay suture was placed in the apex of the heart, which steadied it enough to allow these incisions, which were bleeding, to be closed; the upper one with three interrupted sutures of no. 0 chromic catgut, the lower one by two interrupted sutures of the same material. The pericardium was closed by interrupted sutures of

chromic catgut, leaving about ¾ inch of the lower portion of the incision open, to which, but not through which, a rubber dam drain was connected. The muscles of the wall of the chest were closed with mattress sutures of chromic catgut, and the skin with interrupted silkworm-gut suture. The patient's condition was decidedly improved following operation.

The operation lasted for thirty-five minutes, and as soon as the intrapericardial tension was relieved the pulse became slower and of better quality. The pleural cavity was not opened either by the injury or by the operation.

Course.—The following morning the patient's condition was slightly improved, though he was still in a precarious condition. The pulse was of fair quality, regular and rapid; the temperature was 102 F., and he was still suffering a great deal from dyspnea, the respiratory rate being as high as 40. There was no cough. The dressings were slightly stained with blood. Examination of the blood showed: red blood cells, 3,900,000; hemoglobin, 78 per cent; white blood cells, 6,400; polymorphonuclears, 88 per cent, and monocytes, 12 per cent.

Suddenly that afternoon the patient's condition became worse, with signs of collapse, delirium, cold extremities, a pulse rate of 120 and labored respiration, 60 per minute.

The second day following operation, his condition was about the same: temperature, 103 F.; pulse rate, 120; respiration, 60, and a blood pressure of 130 systolic and 65 diastolic. The wound was dressed and the drain removed. The precordium was pulsating violently. A note made by the medical consultant was as follows: "At the outer border of the heart, there is a friction rub synchronous with respirations and with the heart beat, pleuropericardial. There are dulness over the base of the left lung, bronchial voice and breathing, consolidation and pneumonia in the lower lobe of the left lung."

The third day following the injury, the patient's condition continued the same, with labored respiration. A cough produced thick, yellowish sputum, streaked with blood. That afternoon the respiratory rate reached 70 per minute.

On the fourth day there was well marked dulness at the bases of both lungs, with crepitant râles. The sputum was decidedly rusty. On the ninth day, in his delirium, the patient jumped out of bed and ran the length of the ward. A roentgenogram of the chest on this day showed clouding of the entire right side of the chest, with the exception of small areas at the base and upper lobe of the lung. On the tenth day following admission, the patient's condition was decidedly improved. There were well marked signs over the right side of the chest of a hydropneumothorax, and aspiration produced thick, foul-smelling pus of a chocolate color, together with gas.

On June 15, thirteen days following the injury, the eighth right rib in the posterior axillary line was resected, and the right side of the chest drained. At this time an opening of an abscess on the surface of the lower lobe of the right lung was demonstrated. From that time the patient continued to improve; the temperature dropped gradually, but the respiratory rate stayed above 50 for at least two weeks longer. He was discharged from the hospital, with wounds healed, on July 22, forty-nine days after admission. He was seen two months after discharge, and he had returned to work and was apparently well. Unfortunately, he then disappeared from observation and could not be traced.

COMMENT

Case 2 presents a series of events that are of interest: a stab wound of the heart, which was probably only penetrating, followed by cardiac

tamponade, which was temporarily relieved by aspiration of the pericardial sac, and recurrence of the tamponade followed by pericardotomy and suture of the wounds in the musculature. A stormy convalescence ensued, pneumonitis of both lungs developing and an abscess of the right lung which ruptured into the pleural cavity, producing pyopneumothorax on the right side. The relation of the pneumonia to the injury of the heart is obscure. A roentgenogram of the chest, obtained some hours after the patient received the injury, though a poor film, showed general clouding of the entire left side of the chest. This was not due to hemothorax, as the pleural cavities were not opened at any time. The possibility of a coincident pneumonia has to be considered. The postoperative course of this patient was quite similar to that of a patient whose case was reported by Cole,[1] in whom there were definite physical signs of pneumonia the day following the injury. Recently Cox[2] reported a case that was followed by bronchial pneumonia in the left lung and fluid in both pleural cavities.

In comparing the two cases reported in this paper, it is evident that the type of injury in the first was severe and was not such that the patient could be benefited by operation. The wound in the wall of the chest was large and opened the left pleural cavity. The wound in the wall of the heart was long, perforating and in the vertical axis of the heart. It was situated in the right ventricle, and there was a second long wound in the intraventricular septum. There must have been a decided derangement of the circulation within the heart from the latter opening. There was free bleeding from the wound in the wall of the right ventricle, but no tamponade, as the blood passed directly from the pericardial sac into the left pleural cavity, from whence much escaped through the large wound in the wall of the chest on every respiratory movement. This patient apparently died from loss of blood and intracardial derangement of the circulation.

In case 2, the wound in the wall of the chest was small and did not enter the pleural cavity. Likewise, the opening in the pericardium was small. Though the wounds in the heart were small and nonperforating, they allowed sufficient blood to escape to produce increased intrapericardial pressure and cardiac tamponade. The cardiac tamponade was temporarily relieved by lowering of the intrapericardial pressure by means of aspiration, and it appeared for a time that further surgical intervention might not be needed, for the signs of cardiac tamponade did not reappear until a lapse of from seven to eight hours. Consequently, either the bleeding from the cardiac wound during this period

1. Cole, W. H.: Ann. Surg. **85**:647 (May) 1927.
2. Cox, D. M.: Wounds of the Heart; Report of Two Cases, Arch. Surg. **17**: 484 (Sept.) 1928.

must have been slight, though at operation a fair quantity of blood was found to be escaping from the wound in the wall of the heart, or a clot may have formed which prevented the bleeding for the time being, later becoming dislodged.

Wounds of the heart may be divided into those that only penetrate the musculature and those that perforate and enter one of the chambers. It is evident that the greatest number of cases that reach the surgeon are of the former type.

Perforated wounds are of necessity rapidly fatal, an example being case 1 reported in this paper. Wounds that penetrate the musculature but do not enter one of the chambers of the heart are not as rapidly fatal (case 2), unless a large branch of one of the coronary vessels is involved, for death in these cases is not due to the loss of blood but to the development of a cardiac tamponade, which, though bleeding slowly, may kill in a short period of time, as the pericardial sac is small and the membrane is nonexpansive. The position of the wound in most cases that reach the surgeon is found to be in the left ventricle, as its wall is the thickest, and consequently there is more chance that the wound is merely penetrating in character.

There is little doubt that every person with a wound of the heart should be operated on. This becomes imperative if he shows any signs of approaching cardiac tamponade. However, the aspiration of blood from the pericardial sac may be a life-saving procedure to reduce intra-pericardial pressure temporarily in those cases in which the patient has not been seen until a marked degree of cardiac tamponade has developed, so that time may be obtained to make such preparations as are necessary for surgical intervention.

SUMMARY

Two cases of stab wounds of the chest that involved the heart are reported. In the first there was a perforating wound of the right ventricle which was rapidly fatal as a result of loss of blood. In the second there was a penetrating wound of the musculature of the left ventricle, a cardiac tamponade developing which was temporarily relieved by the aspiration of blood from the pericardial sac; this case later came to operation, and the wound was sutured. The patient recovered, following a stormy convalescence in which pneumonia of both lungs, an abscess of the right lung and empyema developed.

EXPOSURE OF THE HEART TO ATMOSPHERIC PRESSURE

EFFECTS ON THE CARDIAC OUTPUT AND BLOOD PRESSURE

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During the early part of the present century a great deal of attention was focused on the use of a chamber in which negative pressure could be maintained during operations on the chest. Such a chamber was devised by Sauerbruch[1] and was employed extensively in Germany. Subsequently this method was discarded because of the inconveniences which were associated with its use and because a method for inflating the lungs by positive pressure was devised. Recently Beck and his associates in this country have revived interest in the negative pressure chamber as a result of the experimental work that they have performed.

Beck and Cox[2] and Beck and Isaac[3] found that exposure of the heart of the dog to atmospheric pressure caused a rise in the venous pressure, a temporary decline in the arterial pressure and a decrease in the output of the heart. In the experiments of Beck and Cox[2] the output of the heart decreased from 15 to 30 per cent following the opening of the pericardium. Pneumothorax resulted in several of the dogs from the puncture holes in the pericardium. A few of the observations were made on unanesthetized dogs. Ether, amytal, ethyl carbamate or morphine was used as an anesthetic in most of the experiments. The later studies of Beck and Isaac[3] were performed on dogs that were profoundly anesthetized by morphine and sodium barbital. On opening the pericardial cavity to atmospheric pressure, a reduction in the output of the heart equal to 36 per cent of that obtained during the control period occurred. Negative pressure was then applied to the pericardial cavity. This resulted in a reduction of the venous pressure to approximately that obtained in the control period, but the cardiac output did not return nearly to the original level. The increase in the output of the heart was only 14 per cent.

1. Sauerbruch, F.: Ueber die physiologischen und physikalischen Grundlagen bei intrathorakalen Eingriffen in meiner pneumatischen Operationskammer, Verhandl. d. deutsch. Gesellsch. f. Chir. **33**:103, 1904.

2. Beck, C. S., and Cox, W. V.: The Effect of Pericardiostomy on the Mechanics of the Circulation, Arch. Surg. **21**:1023 (Dec.) 1930.

3. Beck, C. S., and Isaac, Leabelle: Pneumocardiac Tamponade: A Study of the Effects of Atmospheric Pressure, Negative Pressure and Positive Pressure Upon the Heart, J. Thoracic Surg. **1**:124, 1931.

If the pressure of the atmosphere were responsible for the decrease in the output of the heart in the experiments referred to, it would appear that the application of negative pressure to the pericardial cavity should result in a return of the cardiac output to the previous level. In an effort to obtain further information on this point, it was decided to repeat some of the experiments of Beck and Isaac under slightly different conditions.

METHOD

Dogs were used in all experiments. Under ether anesthesia the pericardium was sutured to the wall of the chest by the method of Beck and Cox.[2] Following the healing of the incision and after varying intervals of time, the experimental determinations were performed. At least one hour prior to the control studies, the animals were given subcutaneously 0.065 Gm. of morphine. Using local anesthesia, a cannula that was connected to a mercury manometer was placed in the femoral artery for the determination of the arterial blood pressure. Maximum and minimum valves were used. The output of the heart was determined by the Fick principle, which is as follows:

$$\frac{\text{Cubic centimeters of oxygen consumed per minute}}{\text{Amt. oxygen taken up by 1 cc. blood in passing through lungs}} = \text{Cardiac output per min.}$$

The consumption of oxygen was determined by the use of a Benedict spirometer. The arterial sample of blood was obtained from the femoral artery, and the mixed venous sample was obtained by puncture of the right side of the heart. The latter puncture was made through the wall of the chest in getting the blood for the control determinations. Thereafter it was made through the pericardiostomy opening. In some experiments the blood that was removed was replaced by an equal amount. The oxygen content of the blood was determined on the Van Slyke-Neill manometric apparatus.

After the completion of the control determinations, the site of the previous operation was infiltrated with procaine hydrochloride, and an opening 2 cm. square was made in the pericardium. Studies were performed thirty minutes after the pericardium was opened and at varying intervals thereafter. At the completion of the experiments, the animals were killed and autopsy was performed.

RESULTS

In the first two experiments the pericardium was opened two weeks after it had been sutured to the wall of the chest. This procedure was believed to be associated with the production of a pneumothorax. The output of the heart decreased, and the arterial blood pressure declined slightly. It was decided that it was necessary to allow a longer interval of time to elapse between the original operation of suturing the pericardium to the wall of the chest and the pericardiostomy if pneumothorax was to be avoided. The results of an experiment in which it was thought that the incision was accompanied by the entrance of air into the pleural cavity are given in table 1. There was a slight decline in the output of the heart shortly following the incision, which later

TABLE 1.—*The Effects of Pericardiostomy on the Cardiac Output and Blood Pressure* *

Time	Weight, Kg.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maximum Blood Pressure, Mm. Hg	Minimum Blood Pressure, Mm. Hg	Consumption of Oxygen, Cc. per Min.	Cardiac Output per Min., Cc.
Control.................	12.0	18.84	13.28	5.56	163	85	92.46	1,662
30 minutes after pericardiostomy.............	....	20.22	13.68	6.54	163	79	90.41	1,388
1¾ hours after pericardiostomy.............	....	19.80	15.24	4.56	163	79	83.95	1,841

* Jan. 12, 1932: The pericardium was sutured to the wall of the chest.
Jan. 28: Determinations were made. On opening the pericardium a sucking sound was audible. It was feared that the dog got a small amount of air in the pleural cavity.

TABLE 2.—*The Effects of Pericardiostomy on the Cardiac Output and Blood Pressure* *

Time	Weight, Kg.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maximum Blood Pressure, Mm. Hg	Minimum Blood Pressure, Mm. Hg	Consumption of Oxygen, Cc. per Min.	Cardiac Output per Min., Cc.
Control.................	10.0	14.28	7.20	7.08	156	58	78.8	1,113
30 minutes after opening pericardium..........	....	15.22	8.88	6.34	152	60	97.8	1,543
95 minutes after opening pericardium..........	....	15.72	8.86	6.86	124	78	93.2	1,359

* Feb. 11, 1932: The pericardium was sutured to the wall of the chest.
March 9: Studies were performed. The pericardium was securely anchored to the wall of the chest in the neighborhood of the incision. No pneumothorax resulted.

TABLE 3.—*The Effects of Pericardiostomy on the Cardiac Output and Blood Pressure* *

Time	Weight, Kg.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maximum Blood Pressure, Mm. Hg	Minimum Blood Pressure, Mm. Hg	Consumption of Oxygen, Cc. per Min.	Cardiac Output per Min., Cc.
Control.................	14.0	18.48	12.90	5.58	182	96	65.3	1,170
30 minutes after operation..................	....	19.08	15.00	4.08	176	86	80.3	1,968
2½ hours after operation..................	....	18.96	12.80	6.16	193	99	90.4	1,468

* Feb. 10, 1932: The pericardium was sutured to the wall of the chest.
March 11: Studies were performed. At autopsy the pericardium was found to be securely anchored to the wall of the chest. There was no thickening of the mediastinal pleura or collapse of the lungs.

TABLE 4.—*The Effects of Pericardiostomy on the Cardiac Output and Blood Pressure* *

Time	Weight, Kg.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Differ-ence, per Cent by Vol.	Maxi-mum Blood Pres-sure, Mm. Hg	Mini-mum Blood Pres-sure, Mm. Hg	Blood Consump-tion of Oxygen, Cc. per Min.	Cardiac Output per Min., Cc.
Control.	18.0	19.08	13.02	6.06	175	81	108.3	1,787
30 minutes after operation..		18.36	12.86	5.50	172	85	122.0	2,218
5¼ hours after operation		20.04	11.82	8.22	190	101	142.1	1,729

* Dec. 31, 1931: The pericardium was sutured to the wall of the chest.
March 24, 1932: Studies were performed. At autopsy the pericardium was found to be securely anchored at all points adjacent to the incision.

TABLE 5.—*The Effects of Pericardiostomy on the Cardiac Output and Blood Pressure* *

Time	Weight, Kg.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Differ-ence, per Cent by Vol.	Maxi-mum Blood Pres-sure, Mm. Hg	Mini-mum Blood Pres-sure, Mm. Hg	Blood Consump-tion of Oxygen, Cc. per Min.	Cardiac Output per Min., Cc.
Control...	14.2	14.31	10.72	3.62	187	77	89.3	2,467
30 minutes after opening pericardium.........		15.42	10.30	5.12	176	73	116.2	2,270
2½ hours after operation..............		14.10	9.66	4.44	166	86	96.3	2,171
4½ hours after operation.............	....	14.02	9.36	4.66	165	87	94.1	2,019

* Jan. 12, 1932: The pericardium was sutured to the wall of the chest.
March 22: Studies were performed. No opening into the pleural cavity was found at autopsy. Immediately after opening the pericardium a sucking sound was heard, which was believed not to be due to an opening into the pleural cavity but to air entering and leaving the pericardial cavity.

TABLE 6.—*The Effects of Pericardiostomy on the Cardiac Output and Blood Pressure* *

Time	Weight, Kg.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Differ-ence, per Cent by Vol.	Maxi-mum Blood Pres-sure, Mm. Hg	Mini-mum Blood Pres-sure, Mm. Hg	Blood Consump-tion of Oxygen, Cc. per Min.	Cardiac Output per Min., Cc.
Control................	16.1	23.16	18.72	4.44	186	95	177.1	3,989
30 minutes after pericardiostomy............	....	22.92	18.00	4.92	188	95	179.3	3,644

* March 23, 1932: The pericardium was sutured to the wall of the chest.
May 6: Studies were performed. No pneumothorax resulted.

returned to a level that was slightly higher than that existing before. The arterial blood pressure was unaltered. In the remaining experiments from four to ten weeks separated the original operation and the subsequent studies.

In one experiment the animal was not quieted by morphine, and sodium barbital was injected intravenously. A rather marked decrease in the output of the heart was noted following the pericardiostomy. The findings in this experiment are in accord with those of Beck and Isaac.[3]

In the remaining five experiments morphine, supplemented by the local injection of procaine hydrochloride, was used as the anesthetic. The output of the heart in three of the five experiments was found to be greater following the opening of the pericardium than it had been previously, while in two of the experiments it was somewhat lower. In most of the experiments the alterations were probably within the limits of error of the method and of the normal variations in the output of the heart. The maximum and minimum arterial blood pressures remained remarkably constant except for a decline in the maximum pressure and a rise in the minimum pressure shortly before the completion of one of the experiments. The results of these experiments are given in tables 2, 3, 4, 5 and 6.

COMMENT

If a method were available by which the output of the heart could be determined immediately after exposure of the heart to the pressure of the atmosphere, quite likely a decrease in the output would be found. This pressure on the veins at the base of the heart is probably associated with an initial decrease in the amount of blood returning to the heart and hence with a decrease in the cardiac output. The studies reported here indicate that this decrease, if present, is only temporary. If marked disease of the circulatory system were present, it is doubtful if this readjustment would take place. Evidence on this point is lacking, as the present experiments and those of Beck and his associates were performed on normal dogs.

There are several objections to the use of a chamber in which the pressure is maintained at a constant negative level. The negative pressure in the pleural and pericardial cavities is constantly changing, and a large part of its beneficial effect is due to this characteristic. In the chamber that was devised by Sauerbruch the negative pressure was applied to every part of the patient's body surface except for the head and part of the neck. Certainly some of the desirable effects of having a negative pressure at the site of the veins entering the pericardium will be counterbalanced by also having a negative pressure existing around the abdomen and extremities. It is the difference between the pressures existing in the chest cavity and those in the rest

of the body that is important in influencing the return of blood to the heart. It has recently been found by Harrison[4] that the alternate application of positive and negative pressures to all of the body except the head, sufficient to produce overventilation, is associated with a decrease in the cardiac output. The full advantages of the negative pressure chamber would be realized if it included only the chest and if the pressure fluctuated.

SUMMARY

The cardiac output and the maximum and minimum arterial blood pressures of dogs were determined before and after the exposure of the heart to atmospheric pressure. No definite alterations in the arterial pressures were noted, and the changes in the output of the heart were not marked. In some experiments the cardiac output increased slightly, and in others it decreased slightly. Indications for the use of the Sauerbruch negative pressure chamber are not supplied by the results of these experiments on normal dogs. Some of the undesirable features of the apparatus are described.

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4. Harrison, T. R.: Personal communication to the author (1932).

A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomalies.—Friberg[1] reported a case of double kidney in which there were hydronephrosis and a stone in one of the renal pelves. The diagnosis was made before operation. Heminephrectomy was performed, after which the patient recovered.

Rumpel[2] described a case of a one-sided "Langniere," so-called crossed dystrophy, in which the entire fused renal mass was on one side. The lower kidney was pyonephrotic. A median line abdominal incision was made; the destroyed renal segment was resected and removed transperitoneally.

Pierson[3] stated that true unilateral fusion of the kidneys is one of the rarest types of renal anomaly. Morris found only 1 case in 15,908 postmortem examinations, and Steward and Lodge reported 1 in 6,500. In some cases the condition has been observed at birth and in the eighth decade, but it occurs most frequently in the third decade.

The symptoms of this anomaly arise from its complications. Pain is the most common symptom, and may vary from only slight discom-

1. Friberg, Sten: Heminephrektomie bei einer Niere mit zwei Ureteren mit Hydronephrose und Stein im einen Nierenbecken, Acta chir. Scandinav. **69**:393 (March 3) 1932.

2. Rumpel, O.: Nierenresektion bei einseitiger Langniere (gekreuzte Dystopie), Zentralbl. f. Chir. **59**:1290 (May 21) 1932.

3. Pierson, L. E.: Unilateral Fused Kidney, J. Urol. **28**:217 (Aug.) 1932.

fort in the back or abdomen to severe pain, which may resemble that of a calculus, as was demonstrated in Pierson's case. All types of anomalies in fusion are potential factors in the production of dystocia. Because of the fact that true unilateral fused kidneys lie higher in the abdomen than anomalies of the pelvis, there is less tendency for such a complication.

The treatment of this condition, as in the case of any renal anomaly, depends on the complications, such as infection, calculus or other pathologic conditions. In these cases the complication alone is treated. Pierson reported 1 case of unilateral fused kidney, making a total of 103 cases reported in the literature.

[COMPILERS' NOTE.—The clinical symptoms observed in anomalies of the upper part of the urinary tract are important because they may mislead in the diagnosis and, without any evidence of complications or associated pathologic changes, the patients may have severe pain in the back or in the abdomen. The pain may be directly due to pressure exerted by the anomalous organ on surrounding anatomic structures. A urographic examination should be made if the condition is suggestive of a renal anomaly, in an effort to ascertain whether this is present. The treatment should not always be directed entirely to the associated changes, but also to the anomaly itself. In cases of horseshoe kidney, a division of the isthmus and nephropexy at times relieve the clinical symptoms and prevent the occurrence of further changes by securing a better position and better drainage for the organ.]

Stone.—Papin[4] analyzed 136 cases of renal lithiasis. The indications for radical and conservative operation were considered, as well as what he considered the best conservative procedures.

Sixty-five of the 136 patients had had nephrectomy performed, 64 had conservative operations, and for 7 all types of surgical intervention were contraindicated. Successful results were obtained in 56 cases following nephrectomy. Five of the remaining 9 patients died of operative shock resulting from the removal of large infected kidneys; the other 4 patients died of pulmonary congestion, rupture of an abnormal artery and fistula of the small intestine. Nephrectomy was indicated for the following conditions: hydronephrosis, 17 cases; calculous pyonephrosis, 11; coralliform stones, 16; large stones, 6, and multiple stones, 6; pyelotomy was impossible and nephrotomy dangerous in 2. There was 1 case each of atrophic kidney, retrorenal abscess with an infected kidney, pelvic kidney, horseshoe kidney with a fistula, a fistula persisting after nephrotomy, rupture of the ureter and rupture of an abnormal renal vein.

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4. Papin, Edmond: Étude sur la chirurgie de la lithiase rénale et en particulier sur les méthodes conservatrices. Arch. d. mal. d. reins 6:493 (May) 1932.

Four (6.25 per cent) of the 64 patients treated conservatively died; 3 of these deaths were in the series of 12 cases in which nephrectomy was performed, and 1 occurred following pyelotomy with suppuration of the kidney, which required secondary nephrectomy. This case represented 1.9 per cent of the 52 cases in which pyelotomy was performed. Hemorrhage occurred from the wound in 1 case, and there were repeated internal hemorrhages in another case eight and fifteen days after operation. Recurrence of stone on the same side was observed in 5 cases, three, five and six years following operation. and on the opposite side in 1 case ten years afterward. Bilateral calculi occurred in 3 cases. A conservative operation was made possible by a complete roentgenographic examination, with both ascending and descending pyelography, an incision of limited scope, improved methods of suture, drainage of the cavities of the kidney and of the renal fossa and replacement of the kidney by means of nephropexy over pledgets of adipose tissue.

Various types of incisions were used. In 10 cases pelvionephrolithotomy was performed with good results. In several cases the lower pole of the kidney was freely incised and the incision prolonged, when necessary, over the inferior margin of the large lower calyx. In other cases the parenchyma was incised along the oblique fold which forms a continuation of the posterior lip of the hilus. This was done sometimes before and sometimes after the pelvis was opened, and by two different methods: either by a free incision from outside inward, or by passing a blunt Reverdin needle between the posterior surface of the pelvis and the large lower calyx on the one hand and the wall of the sinus on the other, and then through the parenchyma, carrying a silkworm suture which was pulled through the parenchyma. Such an incision seldom bled, and catgut sutures over pledgets of fat gave satisfactory hemostasis. If the pyelonephrotomy was extensive, Papin always sutured the pelvis first, and then the parenchyma above it. In many cases of small stones without much infection the pelvis was left open and the renal area drained. In the majority of cases, transrenal drainage was established. Fixation of the kidney is important. Papin always replaced the kidney in a high position, suspending it hammock-fashion by means of its capsule. Whenever the kidney was movable, nephropexy was performed at the upper pole.

[COMPILERS' NOTE.—In general, the material reviewed by Papin brings out several features of renal lithiasis: 1. Early recognition of the disease is associated with a more conservative operative procedure, which may be undertaken with a slight risk. 2. In a variable number of cases (from 4 to 20 per cent). dependent on the chemical type of calculus and the nature of the infection. renal lithiasis is recurrent,

and prophylactic treatment against recurrence over a period of years must be carefully carried out. 3. The author's advocacy of surgical drainage of the kidney and its fixation in a position to insure adequate physiologic drainage is noteworthy, as these features constitute pertinent factors in restoring the kidney to an uninfected state and to a maximal degree of functional capacity. 4. The selection of cases for nephrectomy or for conservative operation will depend on the operator's surgical judgment in each case. Papin's estimate of good results following nephrectomy fairly well paralleled those in which conservative incisions on the kidney or renal pelvis were undertaken. His criteria for nephrectomy are well founded. Furthermore, they are consistent with the clinical judgment of most urologists, in spite of the present-day well merited emphasis that is being placed by American surgeons on conservative renal operations.]

Scholl [5] reported 2 cases of bacterial concretions in the renal pelvis. In both cases it was possible to obtain cultures of active colon bacilli or a positive culture from any part of the stones, either on the surface or from the cut section. In each case the kidney was either partially or almost totally destroyed and in such a condition that it would have been impossible to obtain permanent cure by attempting to remove the fragments of stone.

With regard to the etiology, it was thought that primarily there was some kind of nucleus, and secondarily that there was some type of cementing process which caused the masses of bacteria to adhere. There seems to be little doubt that the concretions develop by continual proliferation of live bacteria and the addition of cells to the exterior of the growing mass. It is also believed that the presence of necrotic shreds cast from the wall of the renal pelvis in pyelitis may form the nucleus. Many of the patients gave a history of old pyelitis. Some investigators are of the opinion that the first event is simple adhesions of bacteria that form small masses. The most significant factor in these cases seems to be the continuous deposit of bacteria in the renal pelvis.

Heitz-Boyer [6] stated that he has used roentgen rays for some time in operations on the kidney, and wished to extend the practice to operations on the lungs and to fractures. The roentgen rays are indispensable to locate small stones when operating and in cases of multiple calculi to ascertain that none has been overlooked. Some small round stones are known to move freely about in a dilated pelvis, and may even enter the ureter.

5. Scholl, A. J.: Bacterial Concretions in the Kidney Pelvis with Report of Two Personal Cases, Surg., Gynec. & Obst. 55:360 (Sept.) 1932.

6. Heitz-Boyer: Sur la lithiase rénale et sa technique opératoire, Bull. et mém. Soc. nat. de chir. 58:216 (Feb. 13); 386 (March 12) 1932.

Heitz-Boyer expressed the belief that the roentgen ray apparatus should be equipped for taking roentgenograms as well as for fluoroscopic examination, and that it should permit examination at different angles.

Oehlecker [7] reported a case of stones in the kidney which developed after trauma. The patient, a man, aged 45, had suffered a number of fractures and was in bed for some time. A roentgenogram taken at the time of the injury showed no evidence of renal stones. Seven weeks later, symptoms of renal calculus developed. A roentgenogram at that time and at intervals thereafter indicated the definite development of calculi in both kidneys.

The author expressed the belief that the development of stones in this case was due to injury to the kidneys and formation of blood clots in the renal pelvis, which served as a nucleus. Kümmell and Graff have described this condition following renal injury and formation of blood clots. Another type of stone in the kidney develops after extensive injury and fracture of the vertebrae with paralysis of the bladder. In such cases the formation of stone is due to retention of urine in the bladder, causing urinary infection which ascends to the renal pelvis and in that manner forms a stone.

In Walters's [8] review of urologic surgery from the Mayo Clinic for 1931, 60 cases were cited in which stones were removed from the kidney. In many instances the stones were multiple, combined with mild degrees of pyelonephritis or hydronephrosis. In 6 cases plastic operations were performed on the renal pelvis for relief of associated hydronephrosis. Calculi were removed from the ureter by cystoscopic manipulation in 20 cases and by ureterolithotomy in 52. No deaths occurred among the 66 patients from whose kidneys stones were removed; 1 death occurred in the group from whose ureters stones were removed.

Nephrostomy was performed in 27 cases, and pelviostomy in 5, usually as an adjunct to plastic operations on the renal pelvis for hydropnephrosis and for multiple renal calculi associated with renal infection. Nephrectomy was performed in 135 cases. The larger groups included 34 cases in which nephrectomy was performed for removal of a unilateral tuberculous kidney. The kidney was removed in 26 cases because of nephrolithiasis, in 28 cases because of malignant tumors and in 27 cases because of marked unilateral hydronephrosis in which a conservative operation was not warranted. Two patients died fol-

7. Oehlecker, F.: Zur traumatischen Entstehung von Nierensteinen, Zentralbl. f. Chir. **59**:1264 (May 21) 1932.

8. Walters, Waltman: Report of Urologic Surgery (Exclusive of Gynecologic Surgery) for 1931, Proc. Staff Meet., Mayo Clin. **7**:245 (April 27) 1932.

lowing removal of a large adenocarcinoma of the kidney. Three operations were performed in cases of horseshoe kidney, heminephrectomy being done in 1 case, pelviolithotomy in the second and reimplantation of the ureter in the third for the relief of unilateral hydronephrosis. All these patients recovered.

Colic.—Nuvoli and Impiombato[9] reported 150 cases in which there was renal colic and in only 26 of which there was accompanying calculosis, as shown by roentgenograms. In 134 cases there were alterations in the vertebral column. Two types of regional anomaly were found: The twelfth thoracic and first lumbar vertebrae were of a transitional character, or there was sacralization of the fifth lumbar vertebra or lumbarization of the first sacral metamere. Numerical variations were also observed, such as a sacrum with 3, 4 or 6 metameres, and a lumbar spine with 4 or 6 vertebrae. In the cases of spina bifida the neural arch was generally either fissured or entirely wanting. Another type of variation was the prolongation downward, beyond the fourth sacral segment, of the terminal hiatus.

The pathogenesis of the spasms of the urinary passages was undoubtedly associated with these deformities. The majority of the patients had had painful symptoms in the right and then in the left lumbar region, or on one side only, over a period of years. These symptoms often culminated in attacks of colic with diminished urination, vesical tenesmus and terminal hematuria. Clinical study may give negative results or disclose painful points corresponding to the sites of the kidneys and ureters. Urologic examination often yields negative results. Since calculosis also occurs with congenital changes of the spinal column, it may be assumed that one of the pathogenic factors, namely, spasm, is common to both types of cases. In patients predisposed to the formation and elimination of large quantities of salts in general, the stasis produced by spastic contraction in all the urinary passages or at any single point in the tract favors deposition of the salts themselves in the form of calculi. The spastic contractions may last a long time and constitute an almost permanent obstacle to urinary outflow. The malformation of the spinal column seems to be responsible for special nerve changes which create dyskinesia of the urinary passages, leading to chronic stasis and culminating in acute spastic attacks which produce colic.

Either of two hypotheses may be assumed to explain the hematuria often present in these cases of noncalculous colic: The spasm creates acute upward distention, causing rupture of some thin vessel, or spastic contraction at the level of the calices, pelvis or ureter may be sufficient

9. Nuvoli, Umberto, and Impiombato, Gastone: Sindromi di calcolosi urinaria e malformazioni della colonna vertebrale. Arch. ital. d. urol. **7**:589 (July) 1931.

to close the venous vessels and cause engorgement from stasis, with extravasation of blood corpuscles.

Study of the development of the spinal nerves in relation to that of the vertebral column shows that the column evolves parallel to the nerves themselves at about the eighth week; hence every disturbance of the former may reflect on the development of the nerves and their roots. Morphologic changes of the spine at this period will be able to make themselves evident not only on the peripheral nervous system but on the sympathetic autonomic system and its innervations.

[COMPILERS' NOTE.—It is important that urologists, orthopedic surgeons and gynecologists cooperate to clarify the obscure syndromes of colic without calculi, backache, idiopathic hematuria and other urinary symptoms or without definite lesions in the genito-urinary and gynecologic tract. It is obvious that roentgenographic examination in many of these cases may be the means of diagnosis, but the fact must not be overlooked that the pelvis of the kidney is often misplaced and that sometimes the presence of cystine and uric acid stones in the upper part of the urinary tract is not detected by roentgen rays. Many cases have been reported in which the shadow of a stone in the renal pelvis is unusual and situated so close to the spinal column that it is overlooked, and the patient is mistakenly referred to the orthopedic surgeon or the neurosurgeon. A clear description has also been given in the literature, especially by Bransford Lewis, of regurgitation renal colic or the so-called vesicorenal reflux, in which, for lack of a sphincter in the mouth of the ureteral orifice, the vesical contents regurgitate into the kidney, causing sudden renal colic. These urologic problems are always of interest to the urologist, and can be accurately detected by urography.]

Hydronephrosis.—Ceccarelli [10] reported a series of experiments to determine changes that occur in a hydronephrotic kidney after ligation of one or both renal vessels. In experimenting with dogs it was observed that renal function continued for some time after ligation, so that if the ureter were tied also, hydronephrosis could be produced. At the same time sclerosis slowly supervened, invading the entire organ and resulting in vast zones of calcareous infiltration. Adult rabbits were then used for experimentation. After lumbotomy, the ureter was tied about 2 cm. from the pelvis. After from twenty to fifty days a second operation by the abdominal route was performed. It was proved that hydronephrosis had developed in almost every case; the vascular pedicle, or the artery alone in a few cases, was then tied. Laparotomy was chosen as the second type of operation because the right pedicle could be reached without destroying the vascular adhesions established

10. Ceccarelli, G.: Sulle modificazioni delle sacche idronefrotiche dopo legatura del peduncolo vasale. Arch. ital. d. urol. **7**:614 (July) 1931.

between the kidney and the surrounding tissue after lumbotomy. These were particularly important in this case, owing to their relation to the trophism of the organ, in view of the abundance of vessels which the capsule of the hydronephrotic sac possesses.

Necropsy was performed from thirty days to three months after the second operation. The results varied according to the length of time that the hydronephrotic state had existed. The rapid atrophy of the organ was accompanied by sclerosis with calcareous infiltration and osseous new growth. The growth is of a certain biologic interest, since it may possibly be deduced from this that it is independent of the presence of preexistent medullary germs in the kidney, as Sacerdotti and Frattini have contended.

Ceccarelli expressed the opinion that the osseous new growth in his experiments occurred earlier and more rapidly than in normal dogs in which the emulgents had been tied, and that this might bear some relation to the presence of the liquid contained in the pelvis, which was rich in salts of calcium. It was concluded that the ligation of the vascular pedicle of the kidney that had been rendered hydronephrotic caused rapid atrophy of the organ, which became transformed into a small nodule of connective tissue. In the rabbit, in addition to the zones of calcareous infiltration, a typical osseous new growth was produced, whereas the liquid of the sac was totally absorbed.

Moore [11] stated that unilateral renal agenesia occurs infrequently, but the status of the opposite kidney must be determined as a routine measure in any case in which nephrectomy is contemplated. In the conservative treatment of hydronephrosis the merits of the various methods for correcting obstructive conditions at the ureteropelvic juncture must be considered in their application to the individual case at the time of operation. The factor of renal counterbalance is important in unilateral hydronephrosis; experiments on animals have not revealed positive proof as to whether atrophy from disuse of the diseased kidney occurs after the other organ has undergone compensatory hypertrophy.

A case is reported in which was present a large infected hydronephrosis caused by a valvular type of obstruction, with congenital absence of the opposite kidney. The method of relieving the obstruction, together with the functional and urographic end-results, is presented.

Johnson [12] dissected and examined the renal tubules (after the method of Huber) in progressive hydronephrosis in order to determine

11. Moore, T. D.: Congenital Solitary Hydronephrotic Infected Kidney: Pyeloureteroplasty, J. Urol. **27**:581 (May) 1932.

12. Johnson, C. M.: The Pathogenesis of Hydronephrosis, J. Urol. **27**:279 (March) 1932.

what changes occur. Dilatation begins at the glomerulus, and proceeds quickly and evenly to the papillary ducts by the end of two or three weeks. By the end of one month there is beginning atrophy in the glomerulus and proximal convoluted tubules, with some dilatation still present in the distal convoluted and collecting tubules. From this point there are progressive atrophy of the glomeruli and convoluted tubules and progressive dilatation of the collecting tubules in the medulla. By the end of three months some glomeruli may be directly in communication with collecting tubules, owing to the shortening, straightening and disappearance of the convoluted tubules. Others never reach this stage, but undergo atrophy and lose their communication with the collecting tubules after four or five months. A maximal degree of dilatation of the remaining collecting tubules in the medulla is reached at five months. Gradual atrophy and shrinkage in all dimensions then take place.

Cysts.—Jeanneney [13] reported a case in which echinococcus cyst of the kidney was successfully treated by nephrectomy. Hydatid cysts of the kidney are rare and sometimes difficult to diagnose. Of 446 cases of echinococcus disease, Nicaise found that several cysts occurred in 1 kidney alone in 20 cases, that the cysts were bilateral in 12 cases and that the cysts in the kidney were associated with disease in organs such as the liver or the lungs in 58 cases.

The cyst is usually at the level of the superior pole, and at times it may open into the pelvis. It sometimes is well encapsulated and easy to remove. In other cases it is so adherent that part of the renal substance has to be removed with it. Various surgical procedures have been successfully performed, such as marsupialization (sewing of the edges of the cyst cavity to the margin of the incision), puncture of the cyst and drainage, total or partial enucleation and total or partial nephrectomy.

Neff [14] reported a case of massive hemorrhagic cyst in a Wilms tumor. The entire renal mass removed at operation weighed 11 pounds (5 Kg.) and measured 40 by 25 cm. Preliminary aspiration of the contained fluid was done before the removal of the mass. Five solitary cysts larger than the cyst reported by Neff were reviewed from the literature. Cassioli's specimen contained 12 liters; Lockyer's, 25 pints (12.5 liters); Lamson's, 11 to 12 quarts (11 to 12 liters); Krogius' 10 liters, and Archer's, 9 quarts (9 liters). Cassioli's cyst was marsupialized. Nephrectomy was done for the other 4 cysts.

13. Jeanneney, G.: L'échinococcose rénale, Bordeaux chir. **3**:36 (Jan.) 1932.
14. Neff, J. H.: Massive Hemorrhagic Cyst in a Wilms Tumor of the Kidney in an Adult, J. Urol. **28**:65 (July) 1932.

Carbuncle.—Ljunggren [15] stated that carbuncle of the kidney probably occurs more commonly than is indicated by the 50 cases reported in the literature. The diagnosis of this lesion will unquestionably be made more often when symptoms are better known. Renal carbuncle usually results from a break in the fatty capsule with a perinephritic abscess. As a rule, there is a previous history of furuncle or carbuncle. The patient is generally acutely ill with high fever, which may be sustained or intermittent. Urinary symptoms appear only when pyelitis occurs. There is usually pain on the affected side, with tenderness on pressure over the affected area, as well as some spasticity of muscles. Eventual swelling in the flank does not exclude the possibility of carbuncle of the kidney; it generally suggests associated paranephritic abscess. Occasionally, there may be hematuria detectable only microscopically, a few pus cells, a trace of albumin and at times some staphylococci.

It is often difficult to distinguish carbuncle of the kidney from abscess of the kidney, purulent pyelonephritis and formation of pus in the renal hilus. The diagnosis often cannot be made until after an exploratory operation. As a rule, pyelography does not help in making a definite diagnosis, although a case was cited in which deformity caused by pressure of the lower calyx of the right kidney was noted. At nephrectomy the kidney was seen to contain a carbuncle in the lower pole. Although it was known that there was a staphylococcus infection, the pyelogram was the factor aiding in the determination of the differential diagnosis.

Trauma.—Bonhoff [16] reported a case of extensive subcutaneous cross-tear of the kidney, which resulted from a relatively slight injury. The patient struck his back on the edge of a stone wall. Bonhoff attributed the injury not so much to the actual trauma against the wall as to the secondary extensive contraction of the abdominal muscles, which caused a strong hydraulic pressure on the abdominal contents. The injury to the kidney was not a definite tear but, as the author described it, a rupture of the entire renal mass. Early surgical intervention is indicated in these cases, not only to aid in making an accurate diagnosis but to institute treatment before extensive bleeding causes complications. If the injury is extensive, Bonhoff's belief coincides with that of Kümmell, that nephrectomy is the quickest and safest method of treating the condition.

15. Ljunggren, Einar: Beitrag zur Röntgendiagnostik der Nierenkarbunkel, Ztschr. f. urol. Chir. **31**:258, 1932.

16. Bonhoff, Friedrich: Schwere subkutane Nierenzerreibung durch relativ leichtes Trauma, mit Bemerkungen über den Verletzungsmechanismus, Zentralbl. f. Chir. **59**:1331 (May 21) 1932.

Rupture of Renal Artery.— Edmunds [17] reported a case of rupture of a left renal artery following trauma and without injury to the kidney. A man, aged 45, fell about 25 feet (7.6 meters). First aid was given; two hours later the patient was in extreme shock. An exploratory operation by means of a left rectus incision was performed. The spleen was found ruptured transversely. The upper pole lay free in the abdomen; the lower pole was split into two segments, but remained attached to the pedicle. There was a large amount of blood in the abdominal cavity; there was also a subserous hemorrhagic extravasation over almost the entire extent of the descending colon. This was believed to have had its origin from the splenic region and to have gravitated downward behind the peritoneal covering of the bowel. The patient died several days after operation. At necropsy the left renal artery was found to be partly torn across near the aorta, with the formation of a large retroperitoneal hematoma. The artery had become thrombosed, with consequent arrest of hemorrhage.

Aneurysm.—Mathé [18] reported a case of true aneurysm of the renal artery associated with nephrolithiasis, which was secondary to trauma; the condition was successfully relieved by nephrectomy.

Aneurysm of the renal artery is rare, only 56 cases having been reported in the literature. In 40 per cent of 55 cases reviewed there was a history of weakening and injury of the wall of the artery by trauma, and in the remainder a history of severe infections, producing lowered resistance due to sclerosis, fatty degeneration or inflammatory changes of the renal artery. This lesion is difficult to diagnose; only 7 of the reported cases were detected before operation or death. The chief symptoms are hematuria, pain and tumefaction. The hematuria is usually more sudden and more extensive than that caused by other renal lesions. Pulsation and systolic bruit, although rare, are pathognomonic signs. Renal aneurysm should be suspected if there is a ring-shaped, opaque area in the kidney.

The treatment of renal aneurysm is surgical, and operation should be performed as soon as this condition is suspected. Thirty-six untreated patients, whose cases have been reported, died; 16 of the 17 patients on whom nephrectomy had been performed survived. Resection of the aneurysm occasionally is possible. Plastic repair of the aneurysmal sac, drainage of the accompanying hematoma and other surgical procedures less radical than nephrectomy or excision give little, if any, relief.

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17. Edmunds, P. K.: Traumatic Rupture of Left Renal Artery Without Injury to Kidney, J. A. M. A. **99**:467 (Aug. 6) 1932.

18. Mathé, C. P.: Aneurism of the Renal Artery, J. Urol. **27**:607 (June) 1932.

Ptosis. — Braasch [19] stated that renal ptosis without urinary obstruction has no clinical significance and is seldom, if ever, the cause of symptoms. If obstruction exists as the result of ptosis, it can always be demonstrated by urographic or uroscopic examination, and operation is warranted only in the presence of such evidence. In the majority of cases in which nephropexy has been performed without definite evidence of urinary stasis, the symptoms will return within one or two years following operation. Urographic examination after operation is necessary to determine the permanence of a normal renal position as well as improvement in drainage. The percentage of patients having nephroptosis who can be relieved of their symptoms by renal fixation is comparatively small.

[COMPILERS' NOTE.—The recent tendency of American and European urologists again to perform renal suspension or fixation for movable or floating kidney has aroused much controversy. Aside from disputes over differences in various technics for the operation, of which there are many, there has been disagreement as to the indications for the operation. Most authorities believe that nephroptosis is a part of general visceroptosis. Kidd's bizarre concept of an Egyptian type of habitus associated with the condition is in line with this point of view.

Braasch has expressed the opinion of the conservative urologic element with regard to surgical indications in nephroptosis. Doubtless there are cases of floating kidney in which a spastic pelvis or ureter may give pain and in which fixation may bring relief. These, however, must be exceptional. It is well, in general, to take definite evidence of urinary stasis as the criterion for fixation of movable kidney.]

Pregnancy.—Farman and Gummess [20] stated that renal surgery during pregnancy entails a possibility of miscarriage of about 15 per cent, either immediately or before reaching full term. The mortality rate for all types of surgery, including operations on the kidney, during pregnancy is no greater than that for similar procedures in the non-gravid state. Surgical intervention for renal lesions during pregnancy should be limited to cases in which it is necessary for the life or future health of the mother. The most common renal complications of pregnancy requiring operation are renal tuberculosis, calculous pyonephrosis, fulminating pyelonephritis and cortical abscess of the kidney.

19. Braasch, W. F.: Conservation in the Treatment of Movable Kidney, J. A. M. A. **98**:613 (Feb. 20) 1932.

20. Farman, Franklin, and Gummess, K. C.: Surgery of the Kidney During Pregnancy: Report of Case, California & West. Med. **37**:94 (Aug.) 1932.

Foreign Body.—Waring and Drane [21] reported a case of an ascending foreign body in the pelvis of the kidney. The patient, a man, had pain in the right upper quadrant of the abdomen, fever, nausea and vomiting. Examination showed a shadow in the region of the right kidney and pyelonephritis. At operation a foreign body was removed from the right renal pelvis. The calculus was broken while being removed; it was found to be an encrustation of calcium and phosphate on a portion of seed-bearing grass. Several days later another portion of grass and stem was discharged from the wound. Recovery was uneventful. The patient had introduced the grass through the urethra, and a portion had slipped into the bladder. The authors are of the belief that during urination and contraction of the bladder the end of the foreign body was introduced into the ureter and that the sagittate arrangement of the seed on the stem caused it to work its way into the ureter.

Only 2 similar cases have been noted after questioning a group of urologists regarding this condition. Barney reported a case in which a calculus partially surrounding a toothpick was removed from the pelvis of the kidney. Braasch reported a case in which a stone on a hairpin was removed from the ureter; the hairpin had been introduced into the bladder.

Tumors.—Hand and Broders [22] reported an analysis of 193 cases of carcinoma of the kidney. There were 4 grades of malignancy, the basis of which depended on the degree of cellular differentiation in the carcinoma. The grade of malignancy was higher in patients less than 40 years of age. As the degree of malignancy increased, the duration of symptoms decreased; also, as the grade of malignancy increased, the length of postoperative life decreased. In cases in which malignancy was graded 2, 3 and 4, the average duration of life following operation was twice as long as the period over which symptoms existed; in cases in which the malignancy was graded 1, the average duration of life following operation was 3 times as long as the period over which the symptoms existed.

The technical difficulties in removing large carcinomas are important factors in determining immediate mortality. Infection and degeneration are common in large carcinomas. The fact that almost half of the patients operated on died before two years had elapsed makes questionable the advisability of surgical intervention in many cases in which the

21. Waring, T. P., and Drane, Robert: An Ascending Foreign Body in the Kidney Pelvis, Am. J. Roentgenol. **28**:34 (July) 1932.

22. Hand, J. R., and Broders, A. C.: Carcinoma of the Kidney: The Degree of Malignancy in Relation to Factors Bearing on Prognosis, J. Urol. **28**:199 (Aug.) 1932.

carcinoma is large or fixed, or in which the general condition of the patient at the time of operation seems to be below par. Involvement of the renal veins by the carcinoma is a serious complication and increases the technical difficulties of the operation.

One hundred and forty-nine (77 per cent) of the 193 patients who underwent nephrectomy are dead; 44 (23 per cent) are living. Twenty-three (11.9 per cent) of the patients died in the hospital. Of the 126 patients who have died after leaving the hospital, 50 lived less than a year and 66 lived up to twenty-four months. Of the 149 patients who are dead, 97 died in the first five years and 16 died between the fifth and seventeenth years.

Hand and Broders concluded that study of the postoperative results in cases of carcinoma of the kidney, based on the degree of cellular differentiation in the tumor, represents a distinct advance in the knowledge of this disease.

[COMPILERS' NOTE.—Broders' principles of grading the index of malignancy in epithelial neoplasms, based chiefly on cellular differentiation, represent one of the outstanding contributions to pathology of the present day. It is quite natural that this prognostic criterion should be extended to epithelial neoplasms of the kidney, if the principle that lack of cellular differentiation or a preponderance of anaplastic cells in a growth predisposes to a more virulent and more rapid clinical course is sound. Hand and Broders found that there is a distinct clinicopathologic correlation between the grade of malignancy, operability and expectancy of life after operation. This conclusion is consistent with the facts recorded with regard to carcinoma of the skin, the rectum, the bladder and other sites which have been studied thus far.]

Ljunggren [23] stated that there has been considerable literature concerning the relation of tuberculosis to tumors, particularly to carcinoma. The majority of observers maintain that the coexistence of these conditions is only a coincidence. Others are of the opinion that some interrelationship exists between the two lesions: Either the tuberculosis is the primary condition, subsequent to which precarcinomatous changes and a malignant growth develop, or the tumor is the primary factor in the development of tuberculosis, through a lowered general resistance of the body to a tuberculous infection or through the tumor creating a point of lowered resistance in the affected organ.

Ljunggren described a case of tuberculosis and Grawitz' tumor in the same kidney. Seven similar cases have been reported in the literature. According to Ljunggren's point of view, the natural assumption is that it is a coincidence that the two conditions occurred simulta-

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23. Ljunggren, Einar: Tuberculosis and Grawitz's Tumour of the Same Kidney, Acta chir. Scandinav. 69:383 (March 3) 1932.

neously, but the possibility of a renal tumor predisposing to the development of the tuberculous process in the kidney should be taken into consideration.

Evans [24] reported the case of a woman, aged 36, with fibromyoma of the kidney. Symptoms had been present for four years. At operation the tumor was found to have no connection with the pelvic viscera; it was retroperitoneal, and its pedicle was attached to the capsule of the left kidney.

The growth was large and oval, measuring approximately 33 by 23 cm. The surface was roughened but not lobulated. There was a depression at one side, from the center of which radiating lines, resembling bundles of muscular fibers, extended over the surrounding surface. On section the tumor showed an external layer of solid tissue, about 0.5 cm. thick on one side and much thinner on the opposite side; it was pinkish gray and contained a definite nodule, about 1 cm. in length. The central part of the section consisted of a coarse honeycomb structure, the spaces of which were filled partly with mucus and clear fluid. Microscopic examination showed the growth to be a fibromyoma which had undergone extensive liquefactive degeneration.

Barney, Hunter and Mintz [25] stated that radiosensitive tumors described as lymphoblastoma and myeloblastoma are derived from the primitive cells of the lymph nodes, bone marrow and spleen. They are designated radiosensitive because of their response to roentgen rays or radium; for this reason surgery is generally not only contraindicated but futile.

Of 51 cases in which postmortem findings were studied in conjunction with clinical records, there were 39 cases of lymphoblastoma and 12 of myeloblastoma; in 83.3 per cent there were evidences of the disease in the genito-urinary tract.

In any case in which one or another of the tumors is suspected, careful and repeated studies of the blood smears should be made, as well as a careful examination for enlarged nodes, with a biopsy if necessary, and a roentgenologic examination of the chest and spine. The only rational treatment of these tumors is high-voltage roentgen therapy and, in some cases, external applications of radium. This treatment should be instituted as soon as possible after the diagnosis is made. Tumors of this type always cause fatal results. The length of life depends on the type of tumor, on the reaction of the patient to the tumor and on the involvement of vital organs such as the kidneys.

24. Evans, Arthur: Fibromyoma of the Kidney, Proc. Roy Soc. Med. (Sect. Surg.) **25**:333 (Jan.) 1932.

25. Barney, J. D.; Hunter, F. T., and Mintz, E. R.: The Urologic Aspects of Radiosensitive Tumors of the Blood-Forming Organs, J. A. M. A. **98**:1245 (April 9) 1932.

[COMPILERS' NOTE.—Urologists may observe cases of tumors of the blood-forming organs because of a mass in the loin, pain in the back, retention of urine, pyuria, hematuria or priapism. Barney and his associates were among the first to emphasize how important it is for urologists to be ever watchful for tumors of the blood-forming organs when the foregoing signs are noted. The fact that some major involvement of the urinary tract was present in 83.3 per cent of the cases is significant.]

Waterworth [26] stated that giant unilateral renal calculi are rarely observed. Kreutzmann reported removal of a stone weighing 650 Gm., and found in the literature the report of a case cited by Mylvaganan in which a stone weighing 1,140 Gm. was removed at operation; the patient did not survive. The largest stone, weighing 1,130 Gm., was successfully removed by Morrison. Of the 8 cases in which there were unusually large renal calculi, cited by Kreutzmann, the smallest stone, weighing 339 Gm., occurred in the only female in the series.

Waterworth reported the case of a man, aged 64, who had renal pain of many years' duration. He had recently lost 20 pounds (9 Kg.), and a roentgenogram revealed a large, rounded shadow in the region of the right kidney. Nephrectomy was done; the kidney contained a squamous cell carcinoma and a stone 14.5 cm. in diameter and weighing 1,100 Gm. The calculus produced little if any disability in spite of a probable duration of twenty-eight years. The irritation caused by the presence of the stone for such a long time had resulted in the development of an epithelioma of the pelvis of the kidney which recurred following operation and ultimately resulted fatally.

[COMPILERS' NOTE.—A comparatively large number of cases of squamous cell tumors of the kidney, apparently developing secondarily to stones in the kidney, has recently been reported. In most of the cases, as in the one cited by Waterworth, the history suggests that the stones were present for a long time; the majority of the calculi were large and of the staghorn type. Oraison reported the case of a woman, aged 50, whose urinary trouble started with trauma when she was 24 years of age; for ten years preceding operation she had almost constant pain of a type suggesting stones in the kidney. Thomson-Walker cited the case of a man, aged 63, who had passed calculi at intervals for twenty-seven years. Darmady recently reported a case of squamous cell carcinoma in which hydronephrosis was present twenty-eight years before. The size, weight and striking lamellation of the calculus found at operation indicated that the latter had been present many years.

26. Waterworth, S. J.: Giant Renal Calculus; Carcinoma of the Kidney Pelvis. J. Urol. 28:77 (July) 1932.

A review of the reported cases apparently gives justification for suggesting that the majority of stones in the kidney should be removed as early as possible. This should be done not only to relieve pain and to prevent destruction of tissue of the kidney but, as described in the cases heretofore mentioned, to prevent formation of a malignant tumor.]

SUPRARENAL GLAND

Tumors.—Lazarus and Eisenberg [27] stated that tumors of the suprarenal gland are rare. From a clinical and pathologic point of view the most important growths are those arising from the epithelial part of the gland. The outstanding features of tumors involving the cortex are the associated changes in sexual characteristics, most frequently seen among girls. Because the suprarenal medulla is an offshoot of the sympathetic nervous system, tumors arising from this part of the gland bear a close resemblance to tumors of the sympathetic system.

Paraganglioma is composed entirely of mature chromaffin cells of the suprarenal medulla, is usually benign and, unlike other tumors of the suprarenal gland, occurs only in adults. Growths of the suprarenal gland tend to cause irreducible renal ptosis. Fever and cutaneous pigmentation are suggestive symptoms. The presence of a large, ovoid shadow in the roentgenogram, situated over a ptosed and rotated kidney, suggests a tumor of the suprarenal gland.

[Compilers' Note.—Paragangliomas are small tumors consisting of mature chromaffin cells. They are benign and are usually found at necropsy. Usually they are symptomless, the adrenogenital syndrome being absent, as in most suprarenal tumors originating in the sympathetic nervous system. Their occurrence only in adults is a striking contrast to other suprarenal tumors. Fever, cutaneous pigmentation, and the urographic finding of an ovoid tumor situated over a rotated and ptosed kidney are suggestive symptoms. The authors give an excellent review of tumors in general, their relative frequency of occurrence, their histogenesis and their relative malignancy.]

(To be concluded)

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27. Lazarus, J. A., and Eisenberg, A. A.: Tumors of the Adrenal Gland: Report of Two Cases of Paraganglioma of the Adrenal Gland, J. Urol. **27**:1 (Jan.) 1932.

TRAUMATIC OSTEOMYELITIS OF THE CRANIAL VAULT

WITH PARTICULAR REFERENCE TO PATHOGENESIS AND TREATMENT

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LOS ANGELES

Osteomyelitis of the bones of the skull occurs most commonly as a result of inflammatory conditions in the accessory nasal sinuses. Infection of the frontal bone following operative procedures on the frontal sinus has been made the subject of numerous case reports and of several extensive treatises on its etiology, pathology and treatment. Osteomyelitis of the maxilla following antral infections is more rare. True osteomyelitis of the petrous bone and the adjacent occipital bone following disease of the middle ear is probably still more rare, because of the anatomic characteristics of the bone itself.

Traumatic osteomyelitis of the cranial vault has been given but little attention in the now extensive literature dealing with craniocerebral injuries. Could a complete list of such cases be compiled from all sources, it would be considerably more impressive, for individual cases must be more common than might be supposed from a review of the literature. As we have had six cases come to our attention in a series of more than five thousand cases of injury to the head on the neurosurgical service of this hospital, it is our purpose to consider its etiology, pathogenesis and clinical course, and to attempt to deduce therefrom a rational method of treatment. While in some of the cases reported the occurrence of infection is somewhat in the nature of a confession, it has seemed worthwhile, nevertheless, to record our observations.

HISTORICAL NOTE

It is probable that secondary infections of the bones of the skull following injury to the scalp and skull have been observed from earliest times. In spite of the great increase in the number of cases of injuries to the head, the present relative rarity of infections of the bones is to be attributed to the modern prompt and careful treatment of superficial wounds which tend to heal if given an opportunity. A study of the historical references to this condition gives one some insight as to the progress of our knowledge of it. Hippocrates,[1] in his essay "On Injuries of the Head," referred to the extension of the infectious process to the bone from the infected scalp. The principles of treatment of wounds of the head underwent little change through the following centuries as far as the prevention and cure of the infections themselves were concerned. Little is recorded except case reports from the fifteenth to the eighteenth centuries. Percival Pott[2] drew attention to the fact that necrosis and infection of the skull followed local traumatisms. He described two forms of the condition: (1) a localized bony necrosis on which inflammation was engrafted, and probably due to the actual implantation of infectious material in the outer table of the skull through an open wound, and (2) a local necrosis and suppuration with the overlying scalp intact. The latter condition has become known in the surgical literature as "Pott's puffy tumor." His treatment of the inflammatory lesion of the bone was a free removal of bone, especially when pus was present over the dura. Bell,[3] like Pott, was of the opinion that the source of the trouble lay in the separation of the periosteum from the bone, depriving the latter of its blood supply. He also described local suppuration of bone without superficial wounds, and recommended extensive removal of the diseased bone.

Abercrombie[4] described the findings in cases of inflammation of the cranial bones collected from the literature up to his time. In some cases the lesion followed injury, but in none of these was the typical sequence described in which the infection followed open wounds.

With the improvement in the treatment of contaminated scalp wounds with antiseptics and removal of foreign material, secondary osteomyelitis of the skull has become a rarity. In an extensive treatise on injuries of the head, Rawling[5] made no mention of secondary

1. Hippocrates: The Genuine Works of Hippocrates, translated by Francis Adams, London, Sydenham Society, 1849, vol. 1, pp. 454, 460, 461 and 463.

2. Pott, Percival: Chirurgical Works, London, T. Lowndes, 1783, vol. 1, p. 44.

3. Bell, Charles: A System of Operative Surgery Founded on the Basis of Anatomy, London, Longman, Hurst, Rees & Orme, 1807, vol. 1, p. 416.

4. Abercrombie, John: Pathological and Practical Researches on Diseases of the Brain and Spinal Cord, ed. 3, London, Waugh & Innes, 1834, p. 179.

5. Rawling, L. B.: The Surgery of the Skull and Brain, London, Oxford University Press, 1912.

osteomyelitis of the skull. Most modern treatises on surgery are content to advise the removal of gross contaminating material and the use of antiseptics in the prevention of infection, and do not give any description of the condition itself.

ANATOMIC FACTORS

In order to approach the problem of osteomyelitis of the cranial vault properly, it is necessary to review briefly the essential anatomic factors that favor the admission and spread of infection. The rarity of the condition with adequate treatment of open wounds, even in the presence of compound comminuted fractures, speaks well for the natural local defense against such infections. The anatomic factors that need to be elaborated on may be summarized as (1) the character of the bone, (2) its arterial supply and (3) its venous drainage.

Character of Bone.—The cranial vault is formed by the frontal, two parietal, the occipital and the squamous portions of the temporal bones. These bones or portions of bones are composed of two compact layers, a thick and somewhat elastic outer table and a thinner and more brittle inner table, between which a thin layer of cancellous bone, or diploe, is interposed. The internal and external surfaces have a punctate appearance, owing to the points of entrance of fine blood vessels. This is particularly true of the inner table, for the main source of the blood supply of the vault is from the meningeal arteries. This surface is also more irregular, owing to the convolutional markings, the points of special dural attachment and the openings of the emissary veins.

The firmness and thickness of the outer table prevent the ingress of infection when the bone has been exposed by injury even after the periosteum has been scraped off. Were it not for this, osteomyelitis of the skull would undoubtedly be of common occurrence in injuries in which the subaponeurotic space has been opened and infected.

Arterial Supply.—The cranial vault has a double blood supply; a minor external one derived from the small arterioles of the pericranium, especially in the regions of muscle attachments, and a major internal one derived from the meningeal arteries in the dura. The latter consists essentially of the terminal distribution of the middle meningeal arteries, the large size of which indicates that they have a more important function than that of supplying the fibrous dura alone, as Jefferson and Stewart[6] have emphasized. The points of entrance of the terminal arterioles into the inner surface of the bone give it a finely punctate appearance.

It has been a tradition handed down from the time of Percival Pott, that a factor in the production of necrosis is the separation of the over-

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6. Jefferson, G., and Stewart, D.: On the Veins of the Diploë, Brit. J. Surg. **16:**70, 1928.

lying pericranium and underlying dura from a given portion of bone, therefore depriving it of its blood supply. That this is not necessarily the case is the experience of surgeons who have dealt with cranial injuries. In an originally clean, or even in potentially infected, wounds that have been carefully antisepticized, loosened fragments of bone will usually grow and aid in the filling of a defect. Such fragments, of course, are more susceptible to infection, should it develop in a wound, and usually sequestrate, as we shall subsequently show.
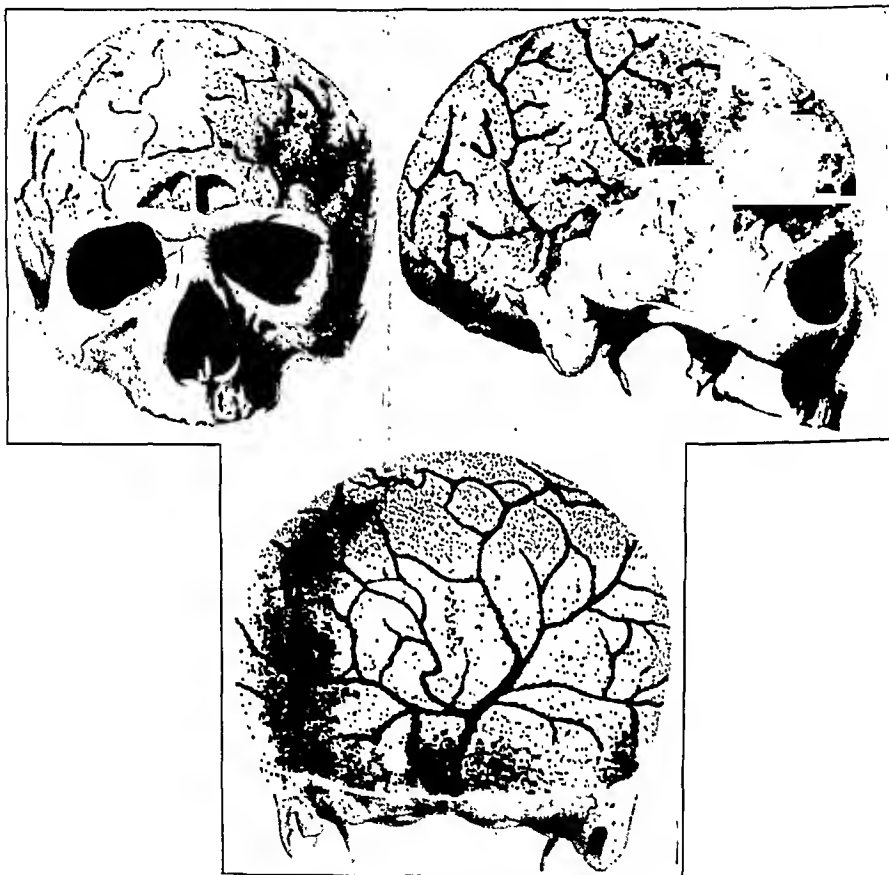
Fig. 1.—Arrangement of the diploic veins in the cranial vault. (After Breschet: Recherches anatomiques, physiologiques et pathologiques sur les canaux veineux des os, 1830.)

Venous Drainage.—The bones forming the cranial vault are drained by an internal system of comparatively large, thin-walled channels in the diploe. In infancy and childhood, these veins form a separate system within the individual bones, but as age advances and ossification of the suture lines takes place, the various systems join to become more or less continuous. In later adult life, these channels are often found to be enlarged and are commonly visible in roentgenograms. There are

three sets of veins on either lateral half of the skull, the frontal, the parietal (consisting of the anterior and posterior temporal veins) and the occipital, draining the bone thus designated (fig. 1). Each group forms a V, with its apex downward. The frontal system drains into the supra-orbital vein, usually in the supra-orbital notch. The antero-temporal vein drains into the sphenoparietal sinus, and the postero-temporal vein into the lateral sinus. The occipital system drains either internally into the lateral sinus or externally into the occipital vein of the scalp. The venous drainage is therefore in a direction opposite to its arterial supply, which comes by way of the anterior and middle meningeal arteries.

In roentgenograms of the skulls of adults, there is frequently seen a network of large diploic veins in the posteroparietal region, which forms the typical "spider" arrangement. This is due to the larger size of the posteroparietal channels, and to their abundant connections with the occipital group. In addition to the progressive enlargement of these channels with advancing age, there are also formed direct communications between the diploic veins and the terminations of the meningeal vessels, probably due to a gradual erosion of the floor of the arterial grooves. These communications may serve as points of entrance of infections into the diploic spaces.

PATHOGENESIS

It was an object of this investigation to study the pathology of osteomyelitis in order to determine the rationality of a plan of treatment that had been elaborated and used with reasonable success. We were denied the privilege of studying either the surgical or the postmortem pathologic changes, because the plan of treatment was essentially nonoperative, and none of the patients died. Therefore, in an investigation of pathogenesis, it was necessary to rely on the clinical course of the disease, information gained from repeated roentgeno-logic examinations and a study of an occasional sequestrum recovered from the draining wound. From these sources of information an attempt has been made to portray the sequence of events that lead to healing of the infection.

Mode of Entrance of Infecting Organism.—There are a variety of ways in which the offending organism gains entrance to the bone, and one may more or less accurately foretell from its mode of invasion the course of the condition, should osteomyelitis develop. In local bruises with or without open wounds, infection is presumably introduced by the traumatic agent, or comes from infected hair follicles. In closed wounds, it may at times be blood borne. Infection may be introduced into the bone when the outer layer has been ground off by scraping or

glancing wounds, often with irregular tearing or avulsion of the overlying scalp. This was the source of the infection in case 3 of our series. In one case (case 4) an operative decompression site for the removal of a subdural clot became secondarily infected from the original adjacent wound in the scalp, with consequent extensive osteomyelitis of the skull. Another common mode of invasion is the development of frank infection in a compound comminuted fracture of the skull, either immediately, or after a latent interval. In another case (case 5) the infection developed after an interval of several weeks, the organism evidently being of a low degree of virulence. As a final possible method of invasion, we find a rather unusual sequence of events in case 6, in which a comminuted depressed fracture of the parietal region was sustained by a fall from a moving automobile. An operation was performed and the depressed fragments elevated. The wound healed by first intention. The child was prone to develop staphylococcus infections of the skin, and some days after the operation numerous small pustules developed over the scalp. Two of these, which were deeper than the rest, resulted in abscesses of the scalp which extended through into the subaponeurotic space, possibly at the site of former bruises. The underlying fragments became secondarily infected and finally sequestrated.

Course of Infection.—The mode of entry of the infecting organism is largely responsible for the lesion produced. Because of the characteristic appearance in the roentgenogram, traumatic osteomyelitis of the skull may be classified as follows:

1. Localized osteomyelitis:
    (*a*) Sclerosing osteitis:[7]

    > (1) Following an open wound of the scalp (Pott's first type of infection of the skull)
    > (2) Following local injury but with the scalp intact ("Pott's puffy tumor")

    (*b*) Circumscribed osteomyelitis:
    > Following direct implantation of infection into the diploe by abrasion of the outer table.

2. Spreading osteomyelitis:
    > Following invasion of the diploic venous channels from a fracture line or operative defect

3. Infectious necrosis of fragments in comminuted skull fracture:
    > Direct or indirect infection of the fragments from a contaminated overlying wound or a secondarily infected operative wound.

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7. It was decided to indicate the two local variations as osteitis and osteomyelitis. In local osteitis, the sclerosing reaction is essentially one of the bony tables, although the diploe are incidentally involved. In circumscribed osteomyelitis the infection is primarily in the diploic spaces rather than in the bone.

Classifications are apt to be incomplete and often imperfect, but the foregoing one seems to answer the purpose so far as our own experience goes. The developmental stages of each type will be considered in turn.

Localized Osteomyelitis.—Under this heading have been included all types of traumatic osteomyelitis which remain as a purely local lesion. They are a response to an ingress of infectious material, which results in a local inflammatory reaction that heals by a sclerotic process, the degree of which depends on the extent of the original invasion.

In sclerosing osteitis of the skull, so well described by Pott, there is an original focus in the bone which is, or becomes, infected, from which the spread is limited. The essential difference in the two varieties is that of the exact means of infection. In the first, the instrument of trauma which cuts the scalp injures the surface of the bone and infects it. The infectious material in this case is therefore inoculated directly into the bone itself. No such case occurs in our series, unless, per-chance, in case 2 a superficial wound was present following the blow on the head. In the second type, known as "Pott's puffy tumor," the injury, again caused by a localized application of force, creates an area of lowered resistance but does not of itself carry in the infectious material. This is often the result of a comparatively minor injury, and the patient may give little or no attention to it at the time. After a variable interval, about a week each in our two cases (cases 1 and 2), a tender, fluctuant swelling develops, which may be incised surgically, or may rupture spontaneously with the discharge of pus. The infecting organism is likely derived from the hair follicles in the overlying scalp, released by the injury, but may be brought to the focus by the blood stream.

In either case, a usually avirulent infection is engrafted on a more or less extensive necrotizing focus at the point of injury. There is an almost coincident development of the protective reaction and the infection, so that the process soon reaches an equilibrium, and there is no further spread of the infection. As a result of a recent surgical experience,[8] it has been learned that there is an active vascular reaction in a

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8. Since this paper was read, we have had the opportunity to study the case of an addtiional patient recently admitted to this hospital. A 59 year old Caucasian man had been injured in an automobile accident on Jan. 1, 1932, sustaining a laceration of the scalp in the left parietal region, a basal fracture of the skull and multiple fractured ribs, with contusion of the lungs. Three and a half months after the injury, a fluctuant and tender swelling of the scalp appeared in the left parietal region at the site of the former laceration. This was incised by an attending physician, with profuse drainage of pus. The wound continued to drain in quantities, and as osteomyelitis was suspected, the patient was sent to the hospital on May 9, 1932, for care. Roentgenograms of the skull revealed an area of mottling about the size of a quarter in the left posterior parietal region.

fairly wide zone about the infected area, though in most cases the infectious process becomes limited in extent. The factors that determine the limits of the spread of the infection are the virulence of the infecting organism, the resistance of the local tissues, as well as the immunologic reaction of the body, and the nature of the minute anatomy of the region thus involved. For instance, if the focus were immediately over a diploic vessel, the lesion might be somewhat elongated, as was apparently the situation in both of the cases of the type in this series (cases 1 and 2). It is not usually a question of a purely peripheral expansion from a central focus, but rather the isolation of a central mass of bone by an encircling process with the ultimate formation of a sequestrum. Healing occurs with the formation of sclerosed bone at the margin of the defect with some variable degree of proliferation of new bone. It is this formation of bone which gives rise to the typical roentgen picture of an increased density of the bone about the defect. The healing process is slow, often a matter of months, with continuous drainage from the overlying sinus in the scalp.

As has been stated, the lesion is likely to remain a local one throughout its course. In case 2, in the adjacent right parietal region, there were found two adjacent areas of rarefaction which were suspected of being extensions (metastases) from the original focus. However, these areas remained more or less unchanged, and at least did not break down, and may have been unrelated lesions. There was no history or evidence of syphilis in the patient. It is theoretically possible for such secondary foci to occur, although we have not had occasion to recognize them with certainty.

The term *circumscribed osteomyelitis* has been retained for another localized type of inflammation. In such cases the infectious material is ground into the diploe with abrasion of the outer table as the result of glancing blows or of scraping the head along the roadway. About each of the infected particles a local infection arises, so that numerous

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While the patient was under treatment right hemiparesis developed rather suddenly, and a few hours later, right-sided jacksonian convulsions made their appearance. As an intracranial extension of the infection was suspected, the area was explored, and a localized extradural abscess was found beneath the area of bone necrosis. Another exploration was carried out two days later because the jacksonian convulsions persisted. A localized, encapsulated, subdural abscess was exposed and drained. The patient died in a few days of a septic meningitis.

Of special interest to us was the condition of the diseased bone. Entirely separated from the adjacent outer table and the underlying diploe was an elongated sequestrum. The surrounding bone and underlying inner table were soft and friable, and when dry, the outer surface of the adjacent skull had a yellowish appearance as though the bone were dead. For a fairly wide zone (about 5 cm.) about the original focus, the outer table "wept" blood, owing to the increased vascularity of the underlying diploic spaces. This was also demonstrated by the profuse bleeding from the opened diploic spaces.

small purulent foci develop. The abraded area becomes involved diffusely first by a confluence of the smaller areas and then by a spread of the process into the adjacent diploe. The outer and inner tables in the regions thus invaded may not be involved, and the only indication of diploic invasion may be a typical mottling as seen in the roentgenogram. Healing occurs by only a minor degree of sclerosis, less marked than in the cases of sclerosing osteitis. Invaded areas of diploe become less mottled and fade away, according to subsequent roentgenograms in our case. If the inner table sequestrates, proliferation from its deeper margins reduces the size of the remaining defect. This regeneration of bone is evidently due to a greater healing activity of the inner table.

In *spreading osteomyelitis* of the skull, the infection begins at a fracture line in the skull, or at the margin of an operative defect (as a decompression opening). It travels along the opened diploic channels, usually in a retrograde direction of the venous flow, i. e., toward the vault rather than the base. This is likely accounted for by stasis of blood in the diploic channels with resulting thrombosis, followed by a retrograde spread of infection, either in the venous channels themselves, or in the diploic spaces about them. When such spaces are followed until two meet, a sequestrum is outlined, being visualized in the roentgenogram by the enlargement and prominence of such spaces. Extension through the inner and outer table from this enlarged channel converts this area into a free sequestrum.

In the third type of traumatic osteomyelitis, infection is superimposed on a comminuted fracture. The process in such cases is fortunately limited by the fracture lines about the fragments; at least, this was what occurred in the cases in our series. Had infection started before reparative processes had begun in the fracture lines of the bones, invasion of the diploic spaces and vessels might have occurred, and a different picture might have been presented. We have as yet seen no such case, but the possibility must be admitted. The process is limited in the surrounding bone, probably by a prompt and active response to the infection. The fragments already separated from their blood supply are more susceptible to the necrosing process, and in fact soon become sequestrums in which degeneration takes place. In one of our cases infection began after fibrous union of the fragments with the adjacent bone had already started.

Formation of Sequestrums.—In any type of traumatic osteomyelitis, sequestrums are likely to be formed. They are often discharged spontaneously, especially if of small size. At times it may be necessary to remove larger ones surgically. The method of formation of sequestrums, as well as their ultimate fate, differs in the various types of osteomyelitis and will be considered separately.

In sclerosing osteitis, although the original necrosis and infection are essentially focal, an elongated sequestrum is usually formed and discharged. This would lead one to the conclusion that the infectious process had spread around and isolated a central island. If this spread occurs in the diploic spaces themselves, one wonders why it is so limited in extent. Furthermore, the sequestrum is elongated, and often remains attached to the adjacent skull by a pedicle at either end, usually toward the base and the vault of the skull. This is evidence that the infection does not spread concentrically and diffusely, but longitudinally and more or less parallel. It may take place along small venous radicals in the diploe.

In circumscribed osteomyelitis, the sequestrum usually consists of fragments of the inner table beneath the abraded area. As shown in our case, the inner table beneath the eroded area becomes isolated by a ring of rarefaction necrosis. This rounded sequestrum may in turn be broken up and discharged. A still different situation exists in spreading osteomyelitis. As shown in our case, the sequestrum is outlined by the infection spreading along the diploic veins, to be separated entirely later when the outer and inner tables over the infected channels become eroded. Invasion of the diploic spaces of the sequestrum then occurs, with more marked destruction of the outer than the inner table. Possibly because of its more abundant blood supply, the inner table escapes except for the erosion of its margins. The conception necessitates a continued attachment of the "sequestrum" to the underlying dura for a variable period following its peripheral detachment. This island of bone becomes, in fact, a sequestrum only when this connection with the dura has been broken. Figures 2 and 3 illustrate the change taking place in the sequestrum in case 4.

When infection occurs in a case of compound comminuted fracture of the vault, particularly before fibrous union has taken place, practically all of the smaller fragments will become infected and form sequestrums. In case 6, one of the larger fragments, being more distantly situated from the source of infection, escaped the process and remained attached to the adjacent skull. Before discharge, a variable degree of necrosis takes place in all sequestrums. In contrast to what occurs in sequestrums secondary to spreading osteomyelitis of the skull, the inner table of such fragments undergoes a greater degree of necrosis than the outer table (fig. 4). This is likely due to the active invasion of the minute perforations of the inner table, points of entrance of the terminal arteries. The outer and more solid surface is less exposed to invasion of the infectious organism.[8a]

8a. Destruction of the inner and outer bony tables does not occur to an equal degree, differing as to both the extent and the table most markedly involved. Cushing (Keen, W. W.: Surgery, Philadelphia, W. B. Saunders Company, 1912, vol. 3,
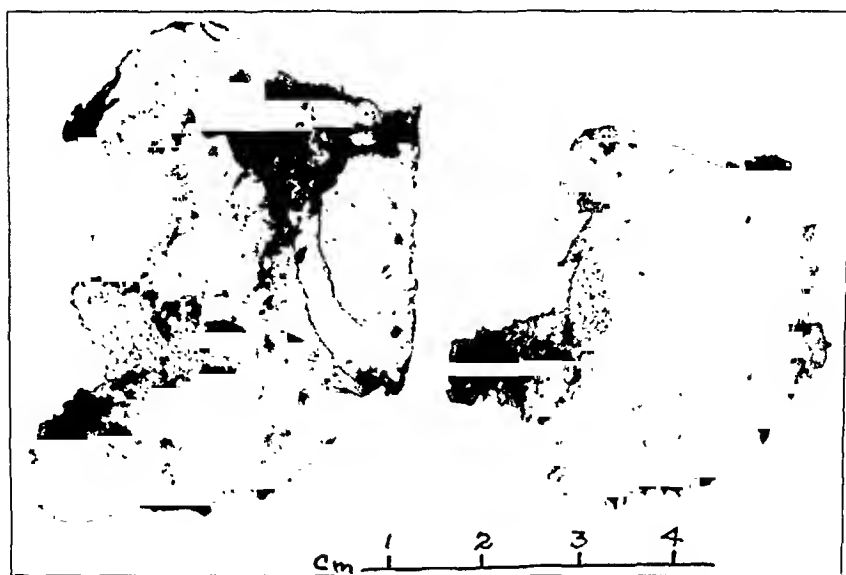
Fig. 2 (case 1).—Sequestrums, showing marked erosion of the outer table which has been completely destroyed on the smaller fragment.
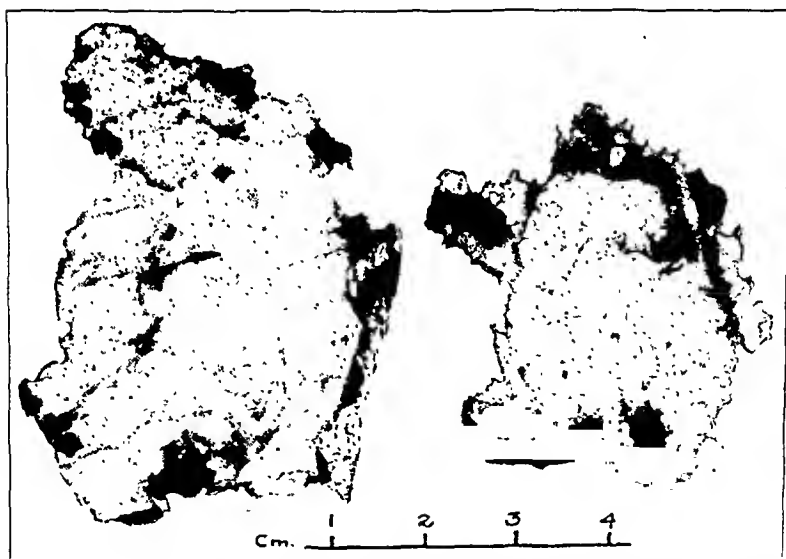
Fig. 3 (case 1).—Sequestrums, as in figure 2, showing the fairly intact inner table. The irregular margins of the fragment are well shown.

In either case, once the sequestrum has formed, the erosion of the margins begins, resulting in an irregular fragment. In instances of localized osteomyelitis this infectious necrosis may occur more or less en masse, owing to the original widespread process. Complete erosion of the bone may occur in circumscribed areas, resulting in holes in the sequestrum which may, by irregular erosion of the margin, become continuous with the margin, further adding to the irregularity of its shape. Why erosion should occur in such spots to this extent may be conjectured as being again due to the peculiarities of the local vascular channel arrangement. This irregular erosion and necrosis may result
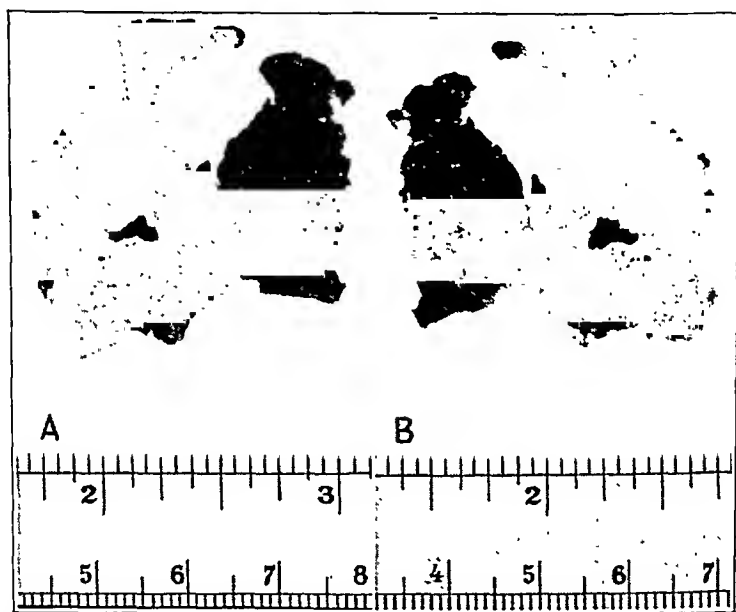
Fig. 4 (case 6).—Sequestrum, showing the outer (*A*) and inner (*B*) surfaces. The outer surface is comparatively smooth, showing little evidence of erosion from this surface. The inner surface shows marked erosion and perforation of both tables from this side.

in the separation of small flakes and fragments from the mother fragment, which may be discharged from the wound, or may undergo complete necrosis in situ.

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p. 49) states that the inner table is often more extensively destroyed than the outer one. This was the situation in case 6, in which an infectious necrosis took place in the larger fragments. In case 4, to the contrary, the outer table of the sequestrums was more extensively necrosed. This difference is probably to be explained largely on the basis of the blood supply. In fragments separated from the dura, necrosis occurs more readily in the inner table, owing to the facility of invasion along the vascular channels perforating the bone. When the dural attachment is retained, the outer table with its comparatively lesser blood supply is more apt to be necrosed.

PATHOLOGY

As has already been stated, it has been impossible to make a study of the pathologic process in our cases, owing to lack of radical surgical measures, and the fact that none of the patients died. It would undoubtedly be enlightening to know the details of the reaction taking place in the adjacent bone in the various types of lesions, which leads to ultimate healing. It will be necessary to refer to the work of McKenzie,[9] who studied the pathologic changes in spreading osteomyelitis of the skull secondary to frontal sinusitis. This type of osteomyelitis is similar to that following trauma. We are in accord with his observations, that the disease does not confine itself to the diploe, but may destroy the solid bone of the tables themselves. It is his opinion that the lesser the blood supply, the more apt the bone is to become infected. This likely accounts for the rapid necrosis of sequestrums when separated from their blood supply.

Laurens [10] found that thrombophlebitis of the diploic veins was found well in advance of the disease of the bone. It seems probable that, as the process is known to spread more actively toward the vault, there is a local thrombosis of the veins at the margin of the infection, with a retrograde extension of the thrombosis, owing to a backing up of the venous current. Infection spreading in this thrombus could easily account for the rapid spread of the disease. It also spreads by direct invasion of the diploic spaces and haversian canals by the infecting organism, a necessarily slower process.

The lesion itself is to be considered, according to McKenzie, as an infectious rarefying osteitis or panosteitis, leading to a more or less extensive destruction of all constituent elements. It may be divided into the following stages: (1) congestion, (2) pus formation in foci in the diploe, (3) diffuse involvement of the entire diploe and (4) penetration of the external and internal tables along vascular channels in the osseous tissue, with ultimate necrosis of the bone. In spreading osteomyelitis of the skull following trauma, there seems to be one essential difference from that secondary to frontal sinusitis. Rapid and direct invasion of the diploic veins takes place, with little lateral extension into the adjacent normal bone. The isolated sequestrum, however, shows evidence (case 4) of active invasion of the diploe and marked destruction of the outer table.   .

In the sclerosing and circumscribed types of traumatic osteomyelitis of the skull, a different picture is presented. In the localized types of osteomyelitis, even though there is no active or diffuse spread of the infection by way of the diploic vessels, engorgement of these vessels

9. McKenzie, Dan: Diffuse Osteomyelitis from Nasal Sinus Suppuration, J. Laryng. & Otol. **28**:6, 79 and 129, 1913.

10. Laurens, quoted by McKenzie.[9]

in the area surrounding the original focus is indicative of an abundant protective reaction. The central zone of inflammation and necrosis breaks down, often with the formation of a central sequestrum. Reaction in the surrounding bone soon develops, and the extent of the inflammation is limited to a variable degree by a sclerosing process. Proliferation of bone at the margin of the defect often reduces it in size. The final stage of the disease is represented by a defect in the skull with an eburnated, rounded margin.

In cases of a superimposed infection on a comminuted fracture of the skull, an interesting pathologic situation exists. Peculiarly enough, active invasion of diploic veins opening into the fracture lines outlining the defect is of rare occurrence. Furthermore, the margin of the bone shows little reaction in this form of sclerosis. The essential lesion is an infection-necrosis of the fragments within the area. If small, practically all of the fragments become readily involved. Some of the larger fragments, especially if at some distance from the point of infection, may escape (case 6). In the larger fragments that become involved, invasion of the diploic venous channels may occur along with erosion of the inner surface and the margins. These processes produce an irregular fragment, which is often broken into several parts before it is discharged.

As illustrated by our cases, it is evident that healing of the external sinuses may occur before all of the smaller sequestrums are discharged. Such fragments undergo necrosis and absorption in situ. Large fragments, however, act as foreign bodies—as sequestrums in other bones—and their presence delays final closure of the draining sinuses.

It must be admitted that other pathologic possibilities may, and likely do, occur. This discussion is necessarily based on the cases at hand, and, for lack of material on which histologic studies might have been made, there undoubtedly exist many gaps in the knowledge of the pathology of this lesion.

Intracranial Complications.—As characteristically seen in localized osteitis of the skull, extradural abscess is the most common intracranial complication. This accumulation of pus is the result of a downward spread of the infection through the inner table. Local dural hyperemia is followed by formation of granulation tissue and exudation of pus. In most instances an extradural abscess is evacuated spontaneously by dissolution of the overlying bone, but on occasion, as Pott himself learned, it is necessary to trephine and drain. This procedure is indicated when evidences of sepsis and localizing neurologic signs make their appearance in a recognized case of osteomyelitis.

In a recently studied case [8] an encapsulated and localized subdural, as well as an extradural, abscess was found and surgically drained. That this does not occur more frequently is in itself evidence of the

protective ability of the dura. Meningitis, sinus thrombosis and cortical and subcortical abscess of the brain are apparently rare complications, unless the infection is carried through the arachnoid and into the brain at the time of injury. It is easily possible for a septic meningitis to develop, should an extradural or particularly a subdural abscess remain undrained for any period of time.

REVIEW OF THE RECENT LITERATURE

There have been but few cases of traumatic osteomyelitis of the skull reported in the past few years. As has been stated, such instances have been sporadically cited in reports on injuries of the head, but case studies have been few in the recent literature. Howard Fleming [11] reported three cases following injury, in two of which the patients were operated on, and all recovered. Shea [12] reported a questionable case in which an injury preceded a frontal sinusitis, and osteomyelitis followed an operation on the frontal sinus. Dabney [13] also reported a case of osteomyelitis of the frontal bone following trauma, with recovery after repeated operations, on which occasions the diseased bone was rongeured away. A similar case was described by Zeno and Cames.[14] Stoian and Costescu [15] recently reported a case in which clinical cure was followed by jacksonian seizures, assumed to be due to some intracranial complication. Dr. Costescu told us that these manifestations were short lived and the patient was soon able to resume his military duties.

Such reports give only a meager insight as to the frequency of the condition, for it is likely that many such cases occur. It would be of interest to know what complications occur; what the mortality is after radical and conservative treatment, and what the duration of the various types of osteomyelitis might prove to be.

Viewed from a roentgenologic standpoint and the clinical course of the disease in the various cases, the following case reports, together with a roentgenographic history of each case, illustrate some of the essential points in the pathogenesis as well as the factors of treatment.

11. Fleming, Howard: Osteomyelitis of the Skull, California & West. Med. **23**:985, 1925.

12. Shea, J. J.: Osteomyelitis of the Frontal Bone: Two Cured Cases, Ann. Otol., Rhin. & Laryng. **37**:500, 1924.

13. Dabney, V.: Osteomyelitis of the Frontal Bone: Report of Four Cases Presenting Problems in Etiology and Treatment, Arch. Otolaryng. **8**:177 (Aug.) 1928.

14. Zeno, L. O., and Cames, O.: Osteomielitis del frontal y absceso extradural con relatión de dos casas personales, Semana méd. **2**:915, 1928.

15. Stoian, C., and Costescu, P.: Osteomielita oaselor craniului si tratamentul ei actual, Rev. de chir., Bucuresti **34**:266 (July-Sept.) 1931.

REPORT OF CASES

CASE 1.—*Sclerosing osteitis of the occipital bone following local injury.*

History.—A musician, aged 22, was admitted to the hospital on March 4, 1929, with the complaint of tenderness and drainage from an "abscess" on the back of his head. He had struck the back of his head about three months previously while working under his car. Shortly afterward, he noticed a swelling with tenderness on the back of his head. This swelling ruptured spontaneously, and a small amount of pus was evacuated. A local physician enlarged the opening and removed a sequestrum, and then sent the patient to the hospital.
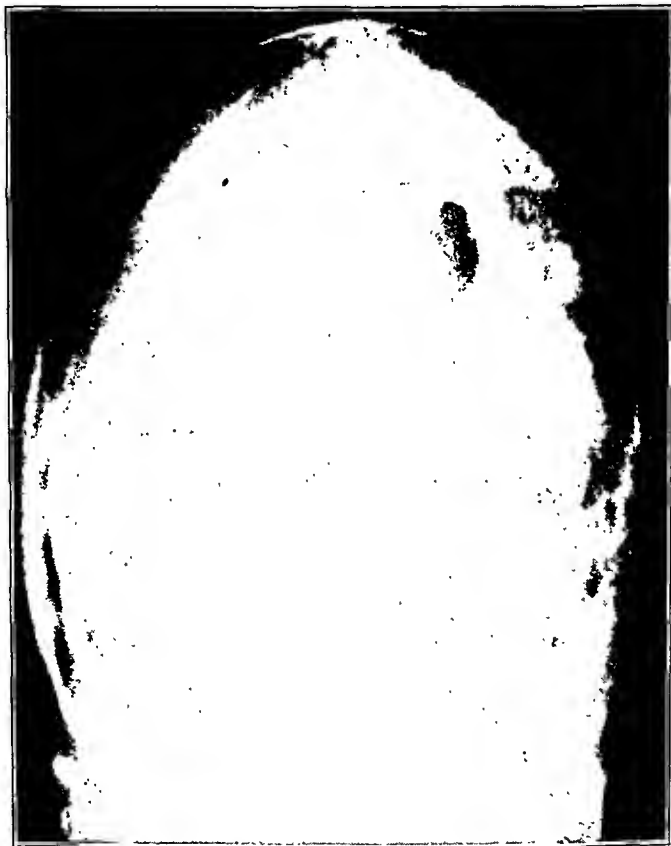
Fig. 5 (case 1).—Roentgenogram, showing sclerosing osteomyelitis in the left occipital region. The bridge between the lighter and darker areas finally sequestrated. It is likely that both tables were involved above, while the outer table alone was involved below.

Physical Examination.—The patient was a well developed and well nourished white man, presenting a draining sinus over the left occipital area about the size of a quarter. There were practically no signs of inflammation locally. The oral temperature was 99 F. Stereoscopic views of the skull revealed a small irregular area of destruction in the left occipital bone near the protuberance.

Course.—A conservative form of treatment was adopted, and the local wound began to close, with a decrease in the amount of drainage. A small sequestrum was removed on April 12. The patient was discharged from the hospital on

April 13, with instructions to return to the outpatient department for observation. He had regular dressings twice a week. Examination of the site of the wound four months later revealed a well healed scar with no drainage.

Course of Lesion Followed Roentgenologically.—At the time of admission, roentgenograms of the skull showed a small irregular area of destruction in the left occipital bone, which had involved both tables (fig. 5). The surrounding bone was thickened and sclerosed. No sequestrums were visualized at this time. On April 8, a second series of pictures revealed a small central sequestrum. As compared with the previous films, the margins of the involved area were smoother and the area was smaller, evidently due to some proliferation of bone in the region. The sequestrum referred to here was removed during the course of dressing the wound on April 12.

With steady improvement and cessation of drainage during the subsequent course of the condition, no further films were taken, and the patient was lost sight of after the wound had completely healed.

Comment.—This is the first example in the series of so-called "sclerosing osteomyelitis" of the skull following a local injury. It would no doubt correspond to "Pott's puffy tumor" of last century's surgical literature. In such cases the sequestrums formed are often discharged spontaneously through the draining wound, operative treatment, therefore, not being required other than the incision of the original swelling. This case ran a comparatively short course as compared with other cases in the series, about nine months in all.

Case 2.—*Sclerosing osteitis of the skull following a blow on the head by falling timber. Long clinical course. Operative removal of central sequestrum and final healing.*

History.—A Mexican laborer, aged 67, was admitted to the hospital on March 18, 1929, with the complaint of local pain and tenderness and a draining wound in the right occipital region. About nine weeks previously he had been struck on the head by a falling timber while at work. This was followed after a week's interval by a large fluctuant swelling at the site of injury. The swelling had been opened by the family physician, and a large amount of pus evacuated. The wound showed no tendency to heal, and the patient finally appeared in the neurosurgical clinic.

Examination.—The patient was a well developed and well nourished Mexican, who presented a profusely draining sinus in the right occipital region with an external opening about the size of a dime. Foul, yellowish pus exuded from this opening. The temperature on admission was 101.6 F. Roentgenograms revealed an irregular localized area of decreased density in the right posterior parietal region with a marked thickening of the surrounding bone suggestive of sclerosing osteitis.

Course.—The customary conservative form of treatment was adopted, with daily dressings with balsam of Peru. Under this regimen, the drainage soon became less profuse, and there was a definite subjective relief of pain and discomfort. The patient was discharged from the hospital on May 17.

The patient was kept under observation for many months, during which the wound was dressed two or three times a week with alcohol or peroxide irrigations, and then treated with mercurochrome-220 soluble. On Oct. 22, 1930, because of the persistence of drainage, the patient was readmitted to the hospital, and the
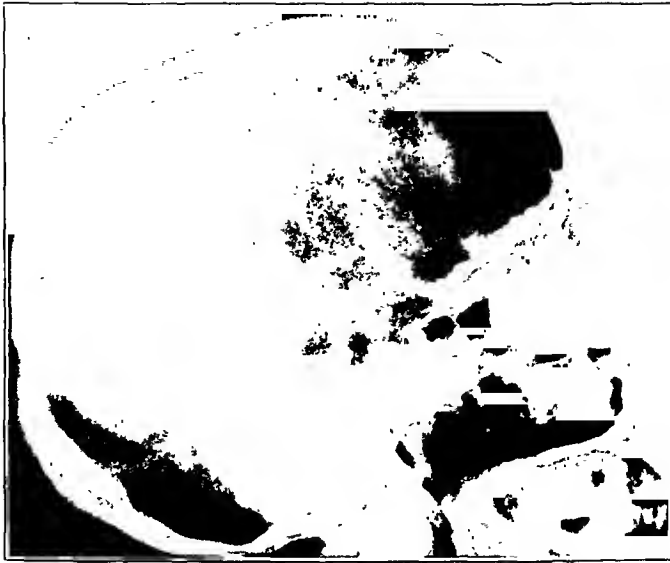
Fig. 6 (case 2).—Roentgenogram, showing area of rarefaction in the right parietal region, possibly an extension of the original focus, seen here outlined on the occipital contour.
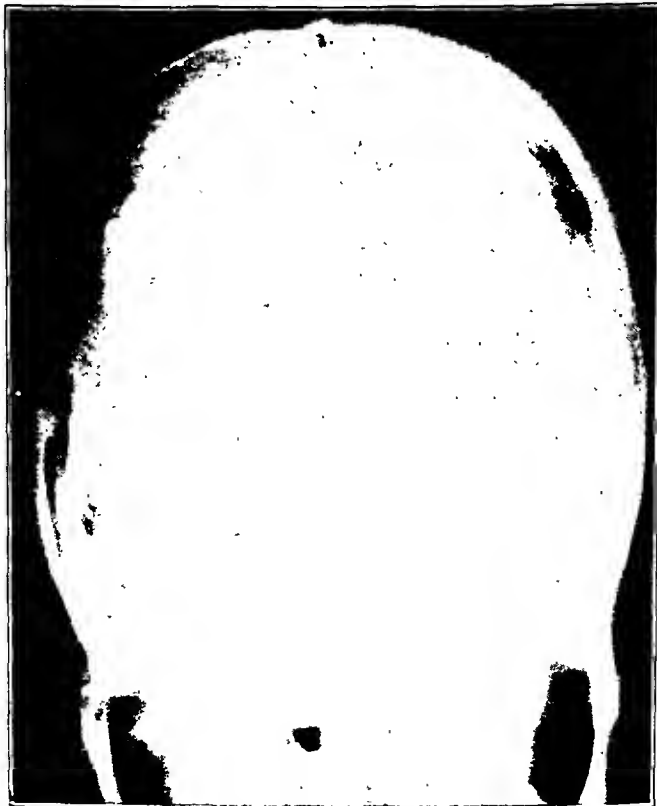
Fig. 7 (case 2).—Roentgenogram, showing sclerosing osteomyelitis of the right occipital region with formation of a central sequestrum.

wound carefully explored (by Dr. Adelstein). A small irregular sequestrum was detached from the margin of the involved area, and the wound incompletely closed, permitting of free drainage. Again daily dressings were made with balsam of Peru until there was but a small amount of drainage from the wound. The patient was discharged to the outpatient department on November 28. He was last seen in the clinic April 18, 1931, when the wound had closed.

Course of Lesion as Seen in Roentgenograms.—The first examinations were made on March 20, 1929, at the time of first admission, when an irregularity of density of the bone was observed in the right occipital region with some thickening of the vault about it. This bony reaction was therefore evident nine weeks after the original injury, and eight weeks after the first evidence of local infection.

A second series of pictures was taken on May 17, two months later, when the same general picture was presented, no sequestrum having formed in the interval. Two other small areas of rarefaction of the vault were found in the right parietal region (fig. 6), and in the line of the parieto-occipital suture. The nature of these rarefied areas was never definitely settled, but the possibility of a regional metastasis of the infection was thought of. These areas did not change during the course of observation, and were present at the time of final discharge. Reexamination on July 30 revealed no change in the condition.

On April 11, 1930, the area of involvement of the bone had become slightly larger, and was then about 5 cm. in diameter. Within this area of moth-eaten appearance, there were some small denser shadows, suggesting that a sequestrum might be forming (fig. 7). There also seemed to be some enlargement of the diploic spaces above and anterior to the area, as though some invasion of these spaces had taken place. On July 9 and October 23, anteroposterior views revealed the slow development of a well outlined sequestrum attached to the surrounding solid bony margin by a narrow pedicle above and below.

The final pictures of the series were taken on Feb. 2, 1931, and revealed the area to be decreased in size with definite sclerosis of the surrounding bone. Some proliferation of the surrounding bone had taken place.

Comment.—This patient had the typical sclerosing type of osteomyelitis of the skull following injury, characterized by a long clinical course and final healing, with sclerosis of the bony margin of the defect. There was some tendency toward filling of this defect by proliferation of the bony margin. Invasion of the diploic spaces was suggested in the roentgenograms on one occasion, which remained localized, due probably to the protective reaction in the bone which developed coincidently with the infectious process. The only recourse to surgical intervention was indicated by the formation of a well outlined sequestrum.

Case 3.—*Circumscribed osteomyelitis of the skull following partial avulsion of the scalp with destruction of a portion of the outer table.*

History.—A mechanical engineer, aged 52, was struck by an automobile while walking down the road. He suffered multiple abrasions and lacerations about the head and face, as well as a partial avulsion of the scalp over the right postero-parietal region. This occurred during the latter part of December, 1929. He was treated by a local physician until his removal to Los Angeles, the details of the treatment not being known. At the time of his admission to the hospital on Jan. 27, 1930, there were considerable local pain and a profuse drainage from the wound, which was opened widely.

Examination.—The patient was a well nourished and well developed white man of middle age, whose general condition seemed to be good; his temperature was normal. A large jagged laceration of the scalp was found in the right postero-parietal region, exposing an area of skull 6 by 8 cm. There was a profuse purulent discharge from the edge of the wound, and the bone itself appeared dark in color. It had a ragged appearance, owing to the irregularities in the exposed diploe, from which pus oozed at numerous points. Stereoscopic views of the skull at this time revealed a circular area of mottling of the bone, 4.5 cm. in diameter, which was diagnosed by the roentgenologist as osteomyelitis of the skull.

Course.—The laceration and the exposed area of the scalp were treated conservatively by daily dressings with balsam of Peru. The subjective symptoms of headache and vertigo (probably posttraumatic in the latter instance at least) soon disappeared, granulations began to fill in the exposed area, and drainage became much less. The patient left the hospital against advice on April 4, going to the

Fig. 8 (case 3).—Local osteomyelitis of the skull following traumatic abrasion of the outer table. The mottled appearance of the area is characteristic.

Veterans' Hospital in Sawtelle, Calif. He remained under treatment in that institution for about a year, where the same sort of treatment with balsam of Peru was carried out. During this interval he was seen twice in our outpatient clinic, on Dec. 6, 1930, and on March 27, 1931, at which times roentgenograms of the skull were taken. At the time of his last visit, the wound had completely closed.

Course of the Lesion Followed Roentgenologically.—The series of x-ray films were taken at the time of the patient's admission on Jan. 27, 1930, and revealed the typical mottled area in the right parietal region characteristic of osteomyelitis of the skull (fig. 8). No sequestrum was demonstrated at this time. The patient left the hospital rather suddenly against advice, and no further pictures were taken at this time. On Dec. 6, 1930, he returned to the clinic, and roentgenograms showed a narrowing of the original area, although its central portion appeared clear, as though a sequestrum had formed and had been discharged or surgically removed. Below and posterior to the original area was another area of equal size, showing a diffuse mottling suggestive of an extension of the infection into

the diploe of this region. The area was irregular in outline, and was limited by the parieto-occipital and the temporoparietal sutures. The reduction in size of the original area appeared to be due to a proliferation of bone from the inner table of the skull. Its margins were rounded, and its increased density suggested an early sclerosis.

At the time of the patient's last visit to the clinic on March 27, 1931, at which time the wound had closed, a right lateral stereoroentgenogram of the skull revealed a progressive narrowing of the original area of osteomyelitis. This was again found to be due largely to the proliferation of bone of the inner table, the defect in the outer table remaining about its original size. The defect in the inner table was 3.5 by 2 cm. in its greatest transverse diameters. The bone about the defect had become thickened and sclerosed. The mottled area previously described below the original area was less conspicuous, healing evidently having been going on.

Comment.—This instance of osteomyelitis of the skull was due to a direct implantation of contaminated material into the exposed diploe of the skull. At the time of admission, almost a month after the accident, the diploic spaces were grossly infected. A more complete follow-up was impossible, owing to the lack of cooperation on the part of the patient, but fortunately he fell into the hands of physicians who gave him the same type of treatment, it having been recommended on his departure. It seems evident that invasion of adjacent diploic spaces may occur to some degree from such a lesion.

CASE 4.—*Spreading osteomyelitis of the vault developing in the margin of an operative defect.*

History.—A white man, aged 36, a painter, was injured when the automobile he was driving was struck by an electric interurban train on the afternoon of March 11, 1928. A wound of the scalp was sutured by the physician rendering first aid. The patient was forwarded to this hospital, where he arrived several hours after the accident.

Physical Examination.—The patient was conscious but rather confused, and there was profuse bleeding from the right ear. A wound 3.5 cm. in length was found in the right parietal area, which had been closed without drainage. The pupils were equal and reacted to light. All reflexes were present and equal on both sides. Lumbar puncture revealed the spinal fluid to be uniformly bloody, and under slightly increased pressure. Flat plates of the skull revealed what appeared to be a linear fracture in the right parietal region, extending downward into the base anterior to the mastoid portion of the temporal bone.

Course.—The patient did fairly well for the following four days, and then a left hemiparesis developed, with clouding of consciousness and an elevation in temperature to 103 F. The deep reflexes on the weakened side were increased over the right, but no Babinski sign or ankle clonus was demonstrated. A right subtemporal decompression was performed twelve days after admission by Dr. George H. Patterson, and a large extradural clot was evacuated. The patient's condition began to improve immediately after the operation. This improvement was short lived, however, for three days later there was a rise in temperature, and swellings of the right elbow, left knee and right sternoclavicular joints made their appearance. It was also noted that the original laceration in the right parietal area was draining a moderate amount of foul-smelling pus. The wound in the scalp was

opened and drainage instituted. The abscesses in the regions of the involved joints were also opened, and culture of the pus showed Streptococcus viridans. The patient's condition again began to improve, in spite of profuse drainage from the incised abscesses and the original wound in the scalp.

The decompression wound in the right temporal region soon became infected secondarily to the original wound in the scalp. This wound broke down completely and drained a yellowish pus in profusion. Because of the persistent drainage from the operative site, osteomyelitis of the underlying skull was suspected, and roentgenograms were taken on May 14, 1928. The films showed a diffuse destruction of bone at the margin of the decompression defect and a marked prominence of the diploic channels posterior to it. The wound was treated conservatively with daily, or even more frequent, dressings with balsam of Peru, which resulted in
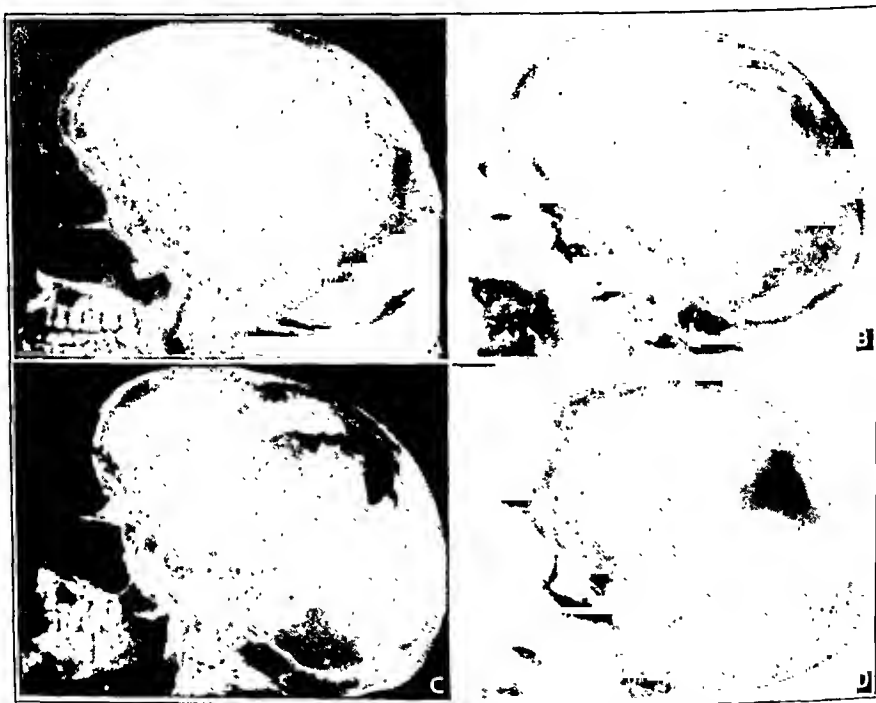
Fig. 9 (case 4).—A, roentgenogram, showing original oblique fracture line, the operative defect and evidence of osteomyelitis following diploic venous channels and mottling of the bone. B, roentgenogram, showing advancing osteomyelitis which is separating a large irregular sequestrum. Smaller sequestrums are formed by the breaking off of the "horns" of the larger fragment. C, roentgenogram, showing the large sequestrum entirely separated, with increasing erosion of its margin. Smaller sequestrums are forming by the breaking off of its margins. D, roentgenogram, showing the irregular defect in the skull left by the removal of sequestrums. There appears to be some proliferation of bone from the inner table in the upper margins of the defect, evidently an attempt to obliterate it.

but little change in the character and amount of drainage. Because of this condition, the patient was kept under observation in the hospital for about a year, when further roentgenograms of the skull were taken (April 15, 1929), which revealed the formation of a large irregular sequestrum above and posterior to the

decompression defect. This was removed surgically by Dr. George H. Patterson on April 24, 1929 (figs. 2 and 3).

The wound continued to drain profusely for several months, but finally began to fill in with granulation tissue, with lessening of the amount of pus. During this interval the wound was dressed daily with balsam of Peru. The patient was discharged to the Veterans' Hospital at Sawtelle, Calif., on Jan. 4, 1930. A letter from that institution dated April 15, 1930, stated that the wound in the skull was still draining. A more recent communication states that the wound healed after the defect in the skull had been closed by grafts by Dr. Eliott Alden.

Course of the Disease Followed Roentgenologically.—The first films were taken on March 12, 1928, immediately after the injury, and revealed a linear fracture extending through the right parietal and temporal bones into the base. The first evidence of osteomyelitis was shown on May 14, 1928, when a right lateral stereoroentgenogram of the skull revealed an extensive and diffuse mottling of the bones of the skull in the right parietal region, marked by definitely enlarged diploic channels extending upward and posteriorly from the decompression defect (fig. 9 *A*). On May 28, 1929, a similar picture was presented, except for the appearance of an irregularly oval area posterior to the operative defect, and connected to the inferior diploic channel. Films taken on Aug. 29, 1928 (fig. 9 *B*), showed essentially the same findings, except for a definite widening of the diploic channels and an increase in the haziness of the bone in the region. Films taken on Dec. 20, 1928, and Feb. 23, 1929, revealed a progressive widening of the diploic channels outlining the sequestrum, with an increasing irregularity of its margins. On April 15, 1929, the sequestrum was found to have separated itself entirely from the surrounding bone, and several smaller fragments had been separated from the larger mass (fig. 9 *C*). There was a large clear area in the upper part of the involved area, as though a considerable portion of the sequestrum had undergone complete destruction. The large sequestrum and several smaller fragments were removed at operation on April 24, 1929. Subsequent right lateral stereoroentgenograms of the skull, taken on June 17, Oct. 1 and Nov. 22, 1929, revealed a progressive rounding off of the margins of the defect, with occlusion of the regional diploic channels, a lessening of the moth-eaten appearance of the skull and an increasing density of the bone forming the margin of the defect (fig. 9 *D*).

Comment.—This is an excellent example of the spreading type of traumatic osteomyelitis of the cranial vault. In this instance, a direct invasion of the diploic channels was possible in the margin of the operative defect in the bone, an unfortunate necessity owing to the occurrence of an interval hemorrhage. The history is that of a slowly developing sequestrum, outlined by converging diploic channels with final separation of the fragment by erosion through the inner and outer tables bounding these channels. Surface interference was limited to simple enlargement of the draining sinuses and removal of sequestrums without interference with the adjacent bony margins in which the battle was still being waged—quite successfully, as time showed. The interval treatment was conservative, with daily dressings with balsam of Peru. Of interest in this case are the metastatic foci elsewhere in the body. McKenzie [9] stated that such foci are not uncommon following traumatic osteomyelitis of the skull, but they are rare following osteomyelitis secondary to suppuration of the frontal sinus.

parietal region. Roentgenograms of the skull revealed a markedly comminuted fracture of the left posteroparietal region of the vault, with depression of several fragments.

Course.—On Aug. 1, 1931, the depressed fragments were elevated and replaced through a semilunar incision (by Dr. Courville), following which the wound healed by first intention. Acute tonsillitis and a pustular infection of the skin of the trunk and of the scalp developed on the fifteenth postoperative day. Two of the scalp foci developed within the region of the operative site, one immediately adjacent to the incision and the second in the midportion of the scalp. The skin incision became infected, broke down and discharged in its lower portion adjacent to one of the local pustules. A second focus developed into an abscess about the size of a half dollar within the tissues of the galea. Smear and culture showed the infecting organism to be Staphylococcus aureus. The location of the draining sinus in the wound, with the amount and persistency of the discharge, gave rise to the suspicion that the infection had gained access to the subaponeurotic space with infection of the bone itself. This was verified by roentgenograms of the skull, which showed the bony margins of one of the large fragments to be hazy and irregular.

The bone was reexposed (by Dr. Courville) through the original incision, and granulation tissue was found extending down to the skull itself. The abscess in the scalp had broken through the galea, and pus was present over the bone, although not in any great quantity. The bone of the major fragments appeared to be normal grossly and union with the surrounding bone had already begun, so it was hoped that the fragments would not be sacrificed. The wound was loosely closed, with drainage in the incision and in the abscess of the scalp. Following the operation there was extensive drainage from all openings. The wound was dressed daily with balsam of Peru. On September 14, a small triangular sequestrum was recovered from one of the sinuses.

Nothing noteworthy occurred in the course of recovery until on Jan. 15, 1932, pain developed in the left ear, followed by rupture of the drum and a purulent drainage. Smear and culture revealed the infecting organism again to be Staphylococcus aureus. The physical condition remained good; there were no unusual elevations in temperature, and the child was able to be up and about the ward. On January 22, an irregular margin of a large sequestrum presented itself at the opening of one of the draining sinuses, and this was removed two days later with little difficulty.

It was thought advisable to give the patient Staphylococcus aureus bacteriophage in an attempt to accelerate healing of the wound. This was given in amounts of from 0.25 to 1 cc. daily. The wound closed rapidly, possibly due to the action of the bacteriophage, but likely also facilitated by the removal of the bony sequestrum. The child was discharged from the service on March 26, with a dry scab over the last of the sinuses, and repeated observations since that time have revealed no tendency toward a recurrence of the infection.

Course of the Lesion Followed Roentgenologically.—The first evidence of infection in the skull was found on Aug. 24, 1931 (fig. 11 *A*), less than four weeks after the injury, and about a week after infection, at which time there was a haziness of the margins of the fragment in the lower portion of the depressed area, with a decrease in density, suggesting osteomyelitis. A small sequestrum was recovered on September 14, probably one of the smaller fragments of the original injury. Left lateral stereograms of the skull, taken on October 24, showed a marked irregularity of the lower fragment with haziness of its substance and an erosion of its midportion. The lower portion of this fragment had become sepa-

rated, so that two small sequestrums were seen in the films. The large sequestrum was still in place at this time. Another series of films taken on Jan. 23, 1932, revealed a forward and downward displacement of the large lower fragment, which was now irregular in contour and presented a large defect in its midportion (fig. 11 *B*). It was one corner of this fragment that presented in one of the sinuses, and which was removed in toto the day following the taking of the roentgenograms. The final pictures were taken on March 23 (fig. 11 *C*), which showed a rounding off of the contour of the bony defect. There were faint shadows in the area, which might have been small sequestrums. It was of interest to note that the upper fragment remained unaffected by the infectious process, and that bony union with the surrounding skull had already begun.
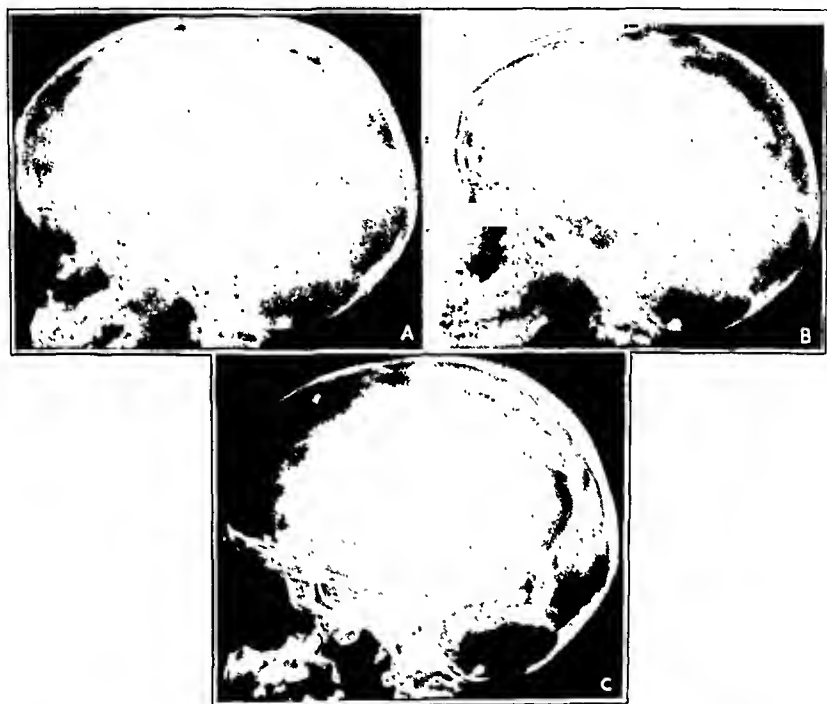
Fig. 11 (case 6).—*A*, osteomyelitis of fragments of bone following comminuted fracture in the left parieto-occipital region. First evidence of infection in the bone, less than four weeks following injury. Invasion of diploic veins of the lower fragment is indicated by irregular lines within its margins. *B*, extensive erosion, fragmentation and dislocation of the original sequestrum. *C*, defect in the skull left by the removal of a large sequestrum. Faint shadows within the outline of the defect suggest that smaller sequestrums may still be present.

Comment.—This case is unusual in that an incidental infection of the scalp in a small patient evidently susceptible to staphylococcic infections was responsible for a rather complicated history of what otherwise might have been a simple case. The condition is probably to be especially classified with case 5, as a modified osteomyelitis of the skull, in

the sense that the process spread in one of the large fragments in a rather typical way. The process did not extend in the surrounding healthy skull, and, peculiarly enough, not in the upper fragment, somewhat more remote from the original infection. With the probability in mind that there was a systemic low threshold of resistance to the staphylococcus, a course of treatment with bacteriophage was instituted. This appeared to hasten the healing process, and it is probably wise in selected chronic cases to use this means in the treatment of the condition.

TREATMENT

The question of radical versus conservative treatment of osteomyelitis of the skull has provoked much discussion and at this time there appears to be a tendency in some clinics to handle such cases in much the same manner as osteomyelitis of the long bones of the body, that is, by early radical surgical intervention. As indicated by a study of the peculiar nature of the bones of the skull, their blood supply and the drainage system and with due appreciation of the opportunity for infection to spread with ease and rapidity through the diploe and enclosed system of veins, it is our opinion that radical surgical intervention has but little place in the treatment of traumatic osteomyelitis of the skull. This is in contradistinction to the principles of treatment of acute osteomyelitis elsewhere in the body, and it is felt that the good results in this series are in no little measure due to the confining of treatment to more or less conservative measures.

Preventive Care.—The prevention of osteomyelitis of the skull is naturally of prime importance and concerns itself mainly with the careful handling and thorough débridement of the wounds in cases of injury to the head presenting compound fractures with indriven fragments of bone and débris from the street. It is necessary to remove all fragments of comminuted bone, hair and other extraneous materials, which always mean potential infection in these cases. A thorough débridement of irregular margins of wounds after the removal of all foreign material will often allow healing per primum. It has also been our practice thoroughly and repeatedly to iodinize all wounds extending through the galea in the course of exploration for underlying fractures.

Plan of Treatment.—When first seen, the active case may present an infected appearing wound of the scalp with irregular edges and draining variable amounts of foul-smelling pus. A roentgen examination at this time will show the type of involvement of the bone present, although it may be anticipated by the history of the case. The local treatment consists of daily dressings with careful cleansing of the wound

and application of balsam of Peru,[16] which in our experience has found a definite place in the therapy of this condition. This substance is slightly antiseptic, keeps the wound moist and favors the formation of healthy granulation tissue. Exuberant granulations that threaten to close draining sinuses should be cauterized with a silver nitrate stick.

The process of sequestration is often slow, and should be checked roentgenologically every three to four weeks. The time of separation of the infected fragments depends on the virulence of the infection and the type of lesion. In some cases the sequestrum is spontaneously discharged, and is found at the time of the daily dressing. If the sequestrum is large, it may be necessary to take the patient to the operating room for its removal. It is necessary to enlarge only the opening of the discharging sinus in order to permit the passage of the bony fragments.

Healing does not take place, as a rule, until all large sequestrums have been discharged or removed. In both of our cases of osteomyelitis of fragments in comminuted fractures healing has occurred with small fragments still being present. It may be justifiable on occasion to remove well formed sequestrums surgically in an attempt to shorten the course of the infection.

At no time, in our opinion, is it warranted or necessary to smooth the surrounding edges of the defect in the skull, as it can be readily seen that this procedure only tends to open widely the diploic spaces and to permit the spread of the infection. In other words, the most rational type of surgical treatment to be employed for traumatic osteo-

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16. The use of balsam of Peru for infections about the head is not a new departure in the field of therapeutics. In 1665, Peter de Marchettis (Med. Chir. 7:11, 1665; quoted by Ballance, C.: A Glimpse Into the History of Surgery of the Brain, New York, The Macmillan Company, 1922, p. 88), reported a case of what seemed to be an extradural and subdural abscess which was treated with this substance after trephining. His description of the case is interesting:

"I remember having a consultation with the famous D. Julio Sala, professor at Pavia, about a man who had been wounded in the head with a dagger. Not only was the bone injured, but the membranes and even the brain. The external wound has been treated by certain practitioners and a cicatrix had formed. After two or three months the patient was troubled with epilepsy and had a fit twice or three times a month. When asked by Professor Sala whether he had ever had an injury to the head, he replied that he had, and pointed out the place. I immediately inserted a probe beneath the crust, and found a penetrating wound, and proceeded at once to operation, and the opening of the parts. The next day I applied the trephine; yellow pus escaped. For 20 days I applied over the brain black western balsam, with the use of which the wound granulated, and in the 30 days the patient was cured of his wound and of his epilepsy."

It is possible that balsam of Peru has been used by others in the treatment of osteomyelitis of the skull, but such reports have not made their appearance in the literature to our knowledge.

myelitis of the skull, under ordinary circumstances, is simple removal of completely detached sequestrums. The occurrence of an extradural abscess that does not drain, or the formation of a secondary subdural abscess, necessitates exploration and drainage, preferably at the site of the original bony necrosis. It may be necessary judiciously to enlarge the opening made by the burr, for an extradural abscess may not be located immediately beneath the area of focal necrosis.

Constitutional Measures.—It is of importance to build up and maintain the resistance of the patient, who usually faces a long clinical course of months with this type of infectious lesion. We have employed the use of such measures as exposure of the body to ultraviolet light or the sun, and the administration of cod liver oil in run-down patients or in the case of children. It is best that such patients be ambulatory, and be permitted outdoors as much as possible. Provided no complications arise, these patients may be treated in the office and, with suitable protection, may carry on their occupations.

Our experience with specific bacteriophage in this condition has been limited to but one case, and no definite opinion can be offered as to its value. In this case (case 6) it seemed rapidly to shorten the course of the infection, although the removal of a remaining large sequestrum also undoubtedly influenced healing to a great extent. This measure should be instituted in well selected cases, for it probably has its place here as in the treatment of other chronic pyogenic infections.

SUMMARY AND CONCLUSIONS

1. Traumatic osteomyelitis of the flat bones of the skull is a somewhat uncommon complication of injuries of the head, judging from the reports in the literature and our own experience. It may be of more frequent occurrence, however, than available information would lead one to believe. It is preventable in many cases by suitable treatment of the original wounds of the scalp.

2. A brief review of the anatomic factors that determine the course of the disease is given. The diploic spaces between the tables, together with the enclosed venous system, favor dissemination of the infection, although early local reaction usually prevents this from taking place.

3. A suggestive classification of the lesion is based on the pathologic changes and the roentgenographic appearance of the lesion: (1) localized osteomyelitis, (2) spreading osteomyelitis and (3) infectious necrosis of fragments in comminuted fracture of the skull. Cases of localized osteomyelitis may be subdivided into (*a*) sclerosing osteitis following local injury with an opened or intact scalp and (*b*) circumscribed osteomyelitis in which infection is implanted directly into the

diploe after abrasion of the outer table of the skull. The type of lesion may be anticipated by recognition of the mode and time of entrance of the infecting organism.

4. The mode of invasion and spread of the infection, together with the probable pathologic change in each type of osteomyelitis, is considered. The pathogenesis of the formation of sequestrums is also discussed.

5. A series of six cases illustrating the various clinical types of the disease is presented. The course of the disease is followed roentgenologically in each case.

6. The plan of treatment has been essentially conservative, consisting of daily dressings with balsam of Peru. This substance favors the subsidence of infection and the development of granulation tissue. It is necessary to keep draining sinuses open by controlling the growth of granulations, a silver nitrate stick being used when necessary. Surgical intervention is limited to the removal of sequestrums that cannot be discharged through draining sinuses.

SNAPPING SCAPULA AND HUMERUS VARUS

REPORT OF SIX CASES

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The presence of friction sounds in the region of the scapula has not gone unnoticed either by the internist or by the surgeon. The daily practice of auscultation of the chest has necessarily led to the discovery and differential diagnosis of sounds extraneous to the pulmonary tissue which might lead to erroneous conclusions. In the literature of the Continent a few articles devoted to a consideration of this subject have appeared in the German, Italian and French languages. In English, however, hardly anything concerning it has come to our knowledge, and we make this our excuse for presenting a brief review of the subject.

Credit for the recognition of this condition must be given to Boinet,[1] who was not able to determine the exact causation of the sound. Some time later Galvagni[2] had the opportunity of observing several phthsical patients in whom scapular sounds were present. He was of the opinion that these sounds occurred in such patients as a result of their general emaciation, and the possible development of a bursa between the muscles of the scapula and the wall of the chest. However, subsequent observations by other authors have demonstrated that scapular grating or snapping may be found in a number of different pathologic conditions, as well as in relatively normal persons presenting no subjective symptoms whatsoever. Indeed, Lotheissen,[3] who interested himself in the mechanism of the production of these sounds and who, by practice, was able to develop them in himself, naively remarked that "with time, one acquires a certain virtuosity in producing noises."

Scapular grating or snapping, the expression of some anomalous condition between the ribs and the undersurface of the scapula, is a tactile-acoustic phenomenon, which has been observed in varying intensity in different persons. In some, there may be a loud snap, clearly audible at a distance of several feet, while in others the noise

1. Boinet: Bull. Soc. de chir. 8:458, 1867; quoted by Küttner, H.: Deutsche med. Wchnschr. 30:534 and 580, 1904.

2. Galvagni, E.: Med. Jahrb., 1873, p. 274.

3. Lotheissen: Med. Klin. 4:51, 1908.

may be reduced to a fine grating sound, barely perceptible to the touch. The intensity of the sound can in no wise be considered as an indication either of the severity of the pathologic condition or of the degree of disability occasioned by its underlying etiologic factors. Mauclaire [4] divided the noises into three main classes: *froissement*, a gentle friction sound, which he considered entirely physiologic in nature; *frottement*, a sound of somewhat louder character, and *craquement*, a loud snapping noise, invariably of pathologic import.

The frequency with which the physiologic friction sounds have been observed appears to vary within a wide range. Bassompierre,[5] in a study of 72 men, noted scapular crepitus as a gentle rustling sound in 51. This crepitus was noted over either the superior or the inferior angle of the scapula and over either half of the body, and apparently bore no relation to age or occupation. Grünfeld [6] found scapular crepitus in 31 of 100 normal people whom he studied. De Laroquette [7] observed scapular crepitus in 8.2 per cent of 620 normal persons. This type of physiologic scapular noise would be of no more than academic interest were it not for the fact that it may be heard quite frequently in tuberculous patients, according to the experience of Kirmisson.[5] From this point of view, the importance of recognizing and differentiating these purely physiologic from pathologic intrapleural sounds is apparent and need detain us no longer than to call attention to their existence.

Our main interest may perhaps better be devoted to the latter two categories described by Mauclaire. A fairly careful review of the literature reveals that cases in which the scapular noise becomes abnormally loud are relatively quite rare. In 18,000 persons, Lotheissen found only 1 case in which the scapular noise could be considered loud, and no case at all in 7,000 patients confined to bed and 40,000 ambulatory patients in which true snapping of the scapula was observed. Similarly, Betke,[8] who had a large military experience, found not a single case of snapping scapula. Nevertheless, a sufficient number of cases have been reported so that some classification has been possible. From a study of these cases, in which either unusually loud scapular noises or snapping was found, it appears that the causes of these sounds may be divided into three main groups:

(*A*) Those due to changes in the bony structure of the undersurface of the scapula, or of the wall of the chest.

4. Mauclaire: Bull. et mém. Soc. d. chirurgiens de Paris **30**:164, 1904; Gaz. d. hôp. **78**:351, 1905.

5. Quoted by Küttner, H.: Deutsche med. Wchnschr. **30**:534 and 580, 1904.

6. Grünfeld, G.: Arch. f. orthop. u. Unfall-Chir. **24**:610, 1926.

7. de Laroquette, M., quoted by Whitman, Royal: A Treatise on Orthopædic Surgery, ed. 9, Philadelphia, Lea & Febiger, 1930, p. 248.

8. Betke: Beitr. z. klin. Chir. **82**:31, 1913.

(*B*) Those due to changes in the musculature intervening between the scapula and the wall of the chest.

(*C*) Those due to changes in bursae normally or abnormally present between the scapula and the wall of the chest.

To these may be added two other groups, which are incapable of proper classification because of a lack of exact knowledge either of the mechanism of production or of the underlying pathology.

In the former of these two groups are several cases in which no reason could be assigned for the production of scapular snapping. Axmann [9] described the case of a girl of 18 who attributed the development of the sound to the carrying of books. X-ray pictures were negative. No treatment was given, because there were no functional disturbances. Betke reported the case of a fusileer, in whom the sound heard at the superior angle of the scapula appeared following musket exercises. Conservative treatment was of no avail, and the patient was finally discharged with a 20 per cent disability. A second case seen by Betke occurred in a man 24 years old, in whom the sound was noticed following the lifting of a weight. At operation nothing, save some possible thinning of the subscapularis fibers, was noted. A four-cornered flap of the trapezius muscle (operation of Mauclaire) was placed between the anterior serratus muscle and the ribs. Both pains and snapping disappeared following operation.

In the latter of these groups is to be placed a not inconsiderable number of cases which appear to be associated with certain occupational activities, such as dressmaking, needle working, piano playing and baking. Whether the noise is to be accounted for by reason of excessive use of the scapular muscles or whether it is to be explained solely on the basis of atrophy of the subscapularis muscle alone cannot be positively determined. Jacoby [10] reported 5 cases appearing in sportsmen. Terrillon [11] reported several cases of this nature. In 1, a baker 20 years old, snapping had been present for about two years. A brace which Terrillon applied for the immobilization of both scapulae restored the patient to full functional capacity. The second case was that of a man, who found it necessary repeatedly to raise his arm forcibly above his head. Snapping, audible at a distance, had been present for from three to four months, and had persisted, despite a change of occupation. Zaphiriadès [12] examined a seamstress, aged 17, with unexplained scapular crepitus and a feeling of oppression between the shoulder blades.

9. Axmann: Deutsche med. Wchnschr. **30**:955, 1904.

10. Jacoby, P.: Ugesk. f. læger **84**:1071, 1922.

11. Terrillon: Arch. gén. de méd. **24**:385, 1874; Bull. et mém. Soc. de chirurgiens de Paris **2**:725, 1876; Bull. gén. de thérap. **46**:8, 1879.

12. Zaphiriadès, A.: Contribution à l'étude du frottement sous-scapulaire, Thèse de Paris, 1903, no. 434.

Though the left scapula was slightly winged, the distinctly audible noise was more intense on the left side. This observation is of interest for the reason that in the presence of a winged scapula there must be predicated a weakness of the very muscles which, by apposing the scapula to the wall of the chest, furnish the mechanical basis for snapping. Doubtless the explanation of this case is to be sought in some anomaly of the soft structures. In the absence of more definite findings, however, it must be left in the category of undetermined etiology.

We have had the opportunity of observing several cases belonging to this undetermined group.

CASE 1.—A. M., a woman, aged 25, a typist, was seen in the outpatient department in the early part of 1929, complaining of pain in the region of the right shoulder, which was made worse on working. The pain radiated from the right scapular region down the whole right arm, and was associated with a markedly uncomfortable grating sound at the upper angle of the scapula, which could be felt and heard on downward motion of the shoulder girdle. The Wassermann reaction was reported as negative, and x-ray pictures showed no evidence of bony abnormalities. The patient disappeared from our observation before anything could be done.

CASE 2.—P. K., a woman, aged 34, a pianist, was first seen in March, 1932, complaining of pain in both forearms. Since the age of 15, she had noted a sense of constriction across the metacarpophalangeal joints on writing and on playing the piano. This sense of tightness was associated with a pain felt mainly along the inner aspect of both forearms and occasionally radiating to the region of the right shoulder and the right middle finger.

Examination disclosed a definite snapping of the scapula on the right side on abduction of the shoulder, with elevation and retraction of the scapula. To a lesser extent, the same was noted on the left side. There was a small area of tenderness over the right pronator radii teres, but no other evidence of neuromuscular involvement. The patient was given diathermy, with no apparent relief, and subsequently disappeared from observation.

The last case is one of more than usual interest because it may throw some light on certain forms of so-called writer's cramp. In an almost identical condition which Galvagni noted, a seamstress of 22 reported that, on attempting to do her work, the fourth and fifth right fingers became extended. There was a loud noise in the region of the inferior angle of the scapula, associated with pain radiating down the neck to the outer side of the arm, and with loss of the power of holding her needle. Examination disclosed an atrophy of the region of the right shoulder, but normal muscular reactions on electrical stimulation. Vesication over the scapula and right shoulder, with a fourteen day period of rest, restored the patient to her normal working capacity. Though unproved, Galvagni was of the opinion that the symptoms might have been attributable to the presence of an abnormally developed bursa in the scapular region, and that many of the cases of occupational cramps associated with pains radiating up the arm were probably to

be explained on this basis. This explanation, however, is purely hypothetic and of interest merely as indicating a method of approach to certain of the cases of occupational cramp associated with scapular grating or snapping.

Excluding these two groups, in which adequate classification is impossible, by far the larger percentage of cases heretofore described can more properly be grouped under the three main divisions noted.

CHANGES IN THE BONY STRUCTURE

In the category of cases due to changes in the bony structure of the scapula or the ribs, a number of subgroups have been noted. The cases in these subgroups may be conveniently divided into those due to:

1. The tubercle of Luschka.
2. Abnormal curvature of the superior angle of the scapula.
3. Exostosis of the ribs or scapula.
4. Tumors of the ribs or scapula.
5. Fracture of the scapula or ribs.
6. Angulation or buckling of the ribs.
7. Tuberculosis or syphilis of the ribs or scapula.

1. The tubercle of Luschka, a small bony or fibrocartilaginous elevation located on the anterior aspect of the superior angle of the scapula, at its largest the size of a pea, usually covered by a bursa, was first described by Luschka [13] and later by von Gruber.[14] Grünfeld found the tubercle present in 7 of a series of 20 cadavers which were selected at random. This percentage, it will be noted, closely approximated the percentage in which he found scapular crepitus in 100 normal people also selected at random, and for this reason he attached great significance to the tubercle as a factor in the production of scapular crepitus. By many, the presence of this tubercle has been considered as solely responsible for the production of snapping of the scapula, especially since resection of this tubercle-bearing area resulted in cure. Heinemann,[15] Volkmann, Lobenhoffer [16] and Huguier [17] each reported cases which would seem to justify this belief. However, in the case which Grünfeld reported, quite the contrary appears to be definitely established. In a woman 32 years old, the pain and noise persisted, even under anesthesia, despite amputation of the tubercle-bearing area, and were obviated only by resection of a strand of the serratus posticus, which was found gray and swollen. The facts in the case would tend

13. Luschka, quoted by Grünfeld.[6]
14. von Gruber: Arch. f. path. Anat. **56**:425, 1872.
15. Heinemann, O.: Klin. Wchnschr. **1**:787, 1922.
16. Lobenhoffer: Beitr. z. klin. Chir. **83**:484, 1913.
17. Huguier, A.: Paris chir. **2**:368, 1910.

rather to support Volkmann [18] and others, who maintained that snapping of the scapula was occasioned by pathologic changes in the scapular musculature rather than by the presence of the tubercle of Luschka. Jastram,[19] too, noted inflammation and degeneration, not only in the region of the tubercle, but at some distance from it, and he expressed the opinion that the snapping resulted from an inequality in the elasticity of the muscle moving over the bursa-covered tubercle, much as a finger plucking a stringed instrument, the chest acting as a resonator. In a case that we observed, we, too, were led to discount the significance of the tubercle.

CASE 3.—S. B., a man, aged 25, a plumber, was first seen in the outpatient department on March 4, 1927, complaining of pain in the region of the right shoulder over a period of several months. This pain was associated with a twitching of the right shoulder and a rough grating sound on motion of the right scapula. There was no history of injury. The patient had been receiving baking and massage without any relief.

On examination it was found that the right shoulder was 1½ inches (3.77 cm.) higher than the left. A slight fulness was found in the suprascapular region, along the upper border of the scapula. There was a slight local tenderness on pressure over this region. There was no limitation of motion in the right shoulder joint, but a marked grating sound was found on downward motion of the shoulder girdle. The posterior edge of the deltoid on the right side was markedly prominent, and there was a continuous fibrillar contraction of the long head of the triceps and deltoid, with marked tenderness over the right trapezius muscles. The patient was given diathermy, roentgen therapy, salicylates, quinine and injections of urea hydrochloride, without relief.

In January, 1931, the patient still complained of needle-like pains in the lower cervical, upper dorsal spine, and especially between the shoulder blades. There was marked crepitation on motion of both scapulae. X-ray pictures showed what appeared to be distinct, rounded, tubercle-like thickening of the upper angle of the scapula. The Wassermann reaction was negative.

When seen in May, 1932, the grating was still present, but the sound produced was not definitely localized to the region of the tubercle and gave the impression of soft tissue crepitus rather than that caused by the rubbing together of two bony surfaces. The patient refused operation and is still under observation.

From what has gone before, it would appear that there is a marked divergence of opinion as to the real importance of the tubercle of Luschka. As in other controversial matters, the truth in all probability lies somewhere in the middle ground. Doubtless there may be some cases in which the removal of the tubercle areas resulted in relief of symptoms. On the other hand, we are supported by competent roentgenologic authority in the opinion that the tubercle exists in a far greater percentage of cases than the presence of symptoms would indi-

18. Volkmann, J.: Klin. Wchnschr. **1**:1838, 1922.

19. Jastram, M.: Deutsche Ztschr. f. Chir. **165**:309, 1921.

cate. And in such event, the conclusion naturally presents itself that the tubercle, even when present, may be of only coincidental significance.

2. The second subdivision is that in which abnormal forward bending of the superior margin of the scapula has been noted. This is apparently of congenital origin, though Lotheissen expressed the opinion that it may be due to the continuous, strong pull of the anterior serratus muscles. The significance of the anterior serratus muscles can easily be demonstrated. In cases of Sprengel's deformity, forward bending of the superior border of the scapula is not unusual, yet it is extremely uncommon to have true snapping of the scapula because of the winging of the scapula. In one case which we had the opportunity of observing, this was clearly shown.

CASE 4.—E. M., a woman, aged 22, who was seen in November, 1929, had first noted weakness of the right shoulder and arm three or four years previously. Within the past two or three weeks she began to complain of a sensation of pain in the left arm and inability to abduct either arm to a right angle.

Examination disclosed a patient of typical acromegalic facies, with moderate exophthalmos. Both arms could be abducted to about 75 degrees. Both scapulae were high and smaller than normal, measuring only 7 inches (17.78 cm.) from the superior to the inferior angle, and presented a marked forward curvature of the superior angles. There was a definite weakness, associated with atrophy, in the right hand, as compared with the left. All deep reflexes of the right extremity were absent, but sensation was apparently normal. As the arms were brought to their limit of abduction, a definite winging of the scapula, due to weakness of the anterior serratus muscle, became apparent. With the arms in the forward position, they could be readily abducted passively throughout the whole range of normal motion, but when the arms were retracted backward, or when the scapulae were pressed against the sides of the chest before attempting abduction, a marked snapping sound, such as is made when running a stick along the stakes of a picket fence, could be heard and felt. At one of the larger neurologic hospitals in the city, a diagnosis of amyotrophic lateral sclerosis was made. In view of the associated neurologic condition no treatment was undertaken.

This case is presented because it may serve almost as a laboratory experiment in elucidating the mechanics of snap production in the usual clinical case. The mechanism of snapping in this case is apparent: a forwardly bent, superior, scapular margin brought firmly in contact with the posterior surface of the ribs, by an external pressure, simulating the action of a normal serratus anticus muscle. The same mechanism may be assumed in the cases reported by Lotheissen, Küttner,[20] de Beule [21] and Schoemaker [22] and in case 5.

20. Küttner, H.: Deutsche med. Wchnschr. 30:534 and 580, 1904.

21. de Beule, in discussion of Hendrix: J. de Chir. et ann. Soc. belge de chir. 7:120, 1907.

22. Schoemaker, J.: Nederl. tijdschr. v. geneesk. 2:744, 1917.

Case 5.—T. R., a girl, aged 18, was seen in the outpatient department of the Hospital for Joint Diseases in February, 1932, complaining of pain radiating down the left shoulder. Three years previously, while running a foot race, she had fallen on her left shoulder and suffered a fracture of the left clavicle, for which she had received inadequate treatment. As a result, she was left with a malunited fracture of the outer end of the left clavicle, and since that time had noticed occasional pain in the left scapular region, with winging of the scapula. There appeared to be no limitation of the left shoulder in any direction.

Examination disclosed the malunited fracture of the left clavicle, which, however, was apparently entirely symptomless. On motion of the shoulder a definite snapping sound was heard and felt in the left scapular region on abduction of the shoulder. The left scapula could easily be heard to make two separate jumps or snaps, with increasing abduction of the shoulder. To our surprise, though the patient complained of no symptoms whatsoever, an almost identical condition was found in the right shoulder, to which no accident had occurred. On the left side
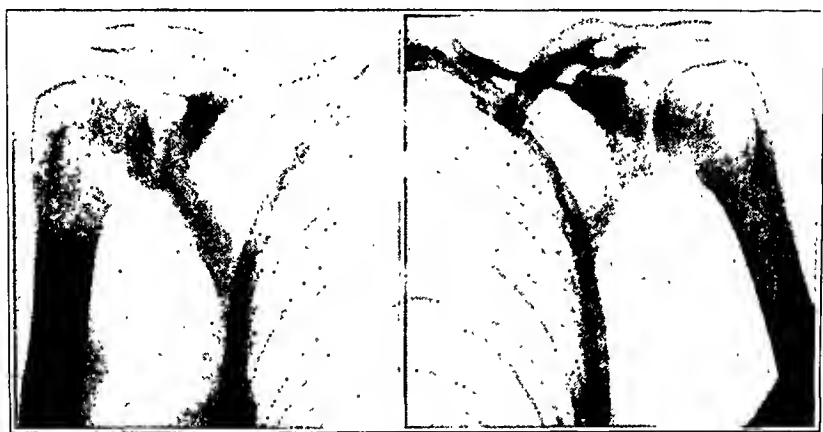
Fig. 1 (case 5).—Roentgenograms, showing bilateral forward curvature of the superior scapular edge, with marked varus of the humeral head.

flexion to 120 degrees, extension to 20 degrees and abduction to 90 degrees produced the sound, while on the right side flexion to 110 degrees, abduction to 90 degrees and even the slightest degree of extension caused the sound to become apparent. The etiologic factor in this case was immediately made apparent on a close study of x-ray pictures of both shoulders. Both showed a marked increase in the normal forward curvature of the superior angle of the scapula, with a peculiar conformation of the humeral head, which will be discussed briefly later (fig. 1).

On February 25, an oblique incision was made over the superior angle of each scapula, and the supraspinous portion of the scapula, from the vertebral border to the superior scapular notch, was resected subperiosteally. The wounds healed well, and motion was begun immediately after subsidence of pain. The resected portions of both scapulae (fig. 2) showed nothing unusual on gross and microscopic examination. Within a period of two weeks the patient was discharged from the hospital, apparently completely cured, but about two months later she returned, complaining of slight pain only in the right scapular region. Examination disclosed

latter sound was in the nature of a soft tissue crepitus, appeared only after operation and disappeared so promptly after the use of diathermy that we believed it to be of the nature of a postoperative traumatic myositis. In this sense it is probably to be grouped with those types of scapular crepitus due to changes in the muscles and will be discussed later.

Finally, this case seemed to us to be of unusual interest, especially to those practicing industrial surgery. It will be noted that the patient correlated and causally connected the snapping with an injury suffered some time previously. Our patient was a young lady of average intelligence and not at all contentious in a medicolegal sense. Still, she assumed, without doubt, that the snapping noise to which her attention was drawn only after the injury to her shoulder was causally related to that injury. A patient need be neither a malingerer nor a neurotic person to infer, incorrectly, a causal relationship between these two coincidental phenomena. Yet, if the patient is either neurotic or a malingerer, it is readily apparent that some difficulty might be experienced in disposing of the case in an equitable manner. To prevent such unpleasantness, x-ray pictures should be taken immediately after the accident. Since the scapular crepitus associated with injury is of the type in which a fracture with malposition of the scapula or the ribs occurs, it is obvious, even in the absence of roentgen findings, that the snapping should be unilateral and localized to the side on which the alleged injury had occurred. In cases in which the snapping is bilateral, the correlation of snapping with the injury should not be entertained. Lotheissen called attention to this point and stressed it, especially in view of the fact that scapular crepitus might be voluntarily produced by a patient intent on a legal suit.

Another case in which scapular snapping associated with forward bending of the superior border was present, but in which the etiology of the snapping could not be definitely determined because operation was not performed, is added for the sake of completeness.

CASE 6.—R. I., a woman, aged 40, a dressmaker, was seen in the outpatient department in February, 1932, complaining of pain in the right scapular region, which radiated down to the right hand. This pain had appeared at irregular intervals during a period of four years. Each attack lasted three or four days at a time and was apparently relieved by diathermy.

The Wassermann reaction was negative. A roentgenogram of the shoulder girdle (fig. 3) suggested a definite increase in the forward angulation of the superior angle of the scapula. There was no limitation of motion in the shoulder, but backward extension of the shoulder and abduction of the right upper extremity caused a mild grating sound, which could be felt and heard in the region of the superior angle. The left scapula was apparently normal. Resection of this portion of the bone was suggested to the patient, but she demurred, and has since disappeared from our observation.

the complete disappearance of the snapping sound previously heard and its replacement by a definite grating crepitus, determinable only by palpation. This yielded readily to the application of diathermy and massage.

Clinically, forward curvature of the superior angle, when present in an abnormal degree, may be demonstrated by grasping the lower end of the scapula, forcibly retracting it from the wall of the chest and then palpating along the upper portion of the vertebral border. When the curvature itself cannot actually be felt, an impression of increase in the thickness of the superior angle may be obtained, which can then be checked by x-ray pictures. Roentgenographically, we have best been able to demonstrate the condition by oblique views of the shoulder. In such an angle, the abnormal forward bending of the superior margin can best be seen. But even when this cannot definitely be determined,
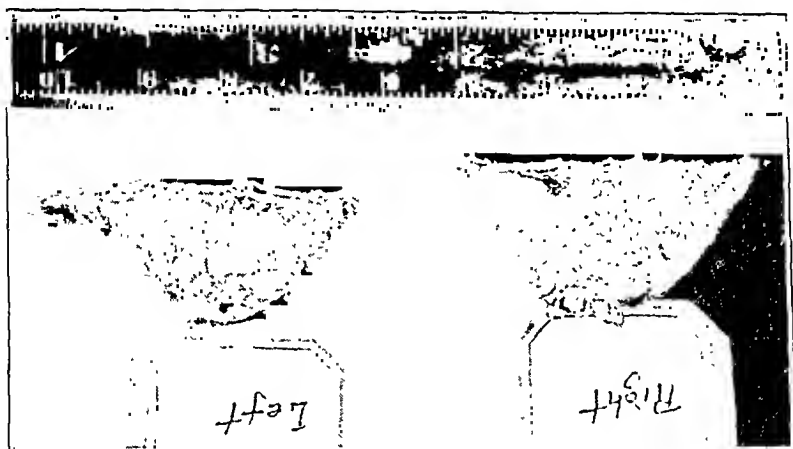
Fig. 2.—Supraspinous portions of the scapula, removed at operation.

other evidence may be at hand. Attention has been called to the fact that an abnormal curvature may be suspected when the line of the superior margin of the scapula tilts downward toward the glenoid fossa and makes a sharply acute angle with the line of the superior margin of the acromion and spinous process of the scapula, instead of being nearly parallel with it.

Case 5 appeared to be of more than usual interest for several reasons. It demonstrated quite conclusively the significance of the increased curvature of the upper portion of the scapula in the production of snapping, with the subsidence of symptoms following removal of the offending portions of bone. It was of interest further in that the patient presented two types of scapular sound, one of which was to be explained on the basis of the anomalous curvature noted in the superior angle of the scapula, the other of which developed after operation and was, we believe, of an entirely different nature. The

3. The third subdivision is that in which scapular snapping is noted in the presence of exostoses on the ribs or on the undersurface of the scapula. Some authors seem to think that there is no definitely established relationship between the presence of an exostosis and the development of scapular snapping. However, Demarquay,[23] Zieschang,[24] McWilliams.[25] Betke, Brown,[26] Goldthwaite.[27] Görres [28] and others have reported cases in which removal of the portion of the scapula bearing the exostosis resulted in cure of the condition. The exostosis may
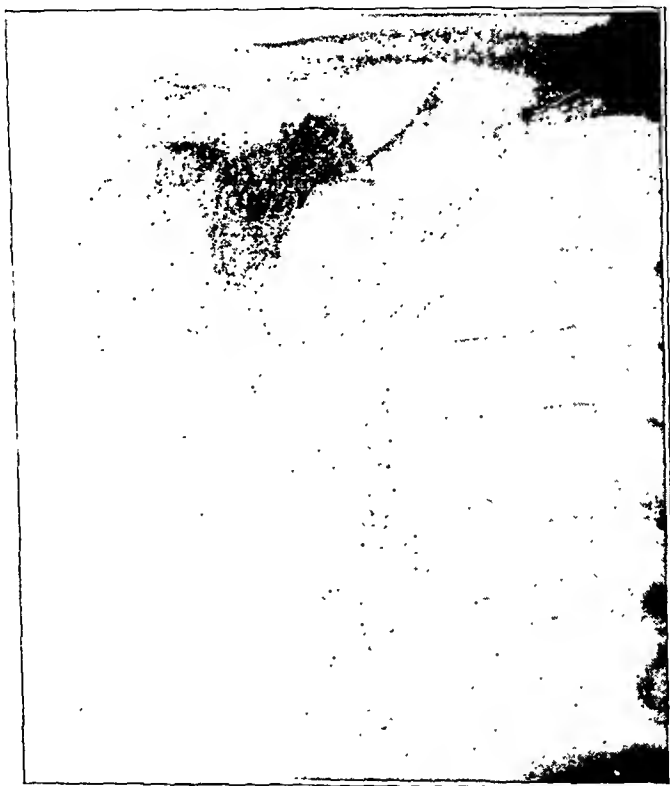
Fig. 3 (case 6).—Roentgenogram, showing forward angulation of the superior scapular margin.

be found either at the superior or at the inferior angle of the scapula and may vary in size from osteocartilaginous nodules to relatively large mushroom-shaped masses.

23. Demarquay, quoted by Küttner;[20] quoted by Grünfeld.[6]

24. Zieschang, Karl: Ueber das Scapularkrachen, Leipzig, B. Georgi, 1907; quoted by Ssoson-Jaroschewitsch, A. J.: Arch. f. klin. Chir. 123:378, 1923.

25. McWilliams, C. A.: Scapular Exostosis with Adventitious Bursa, J. A. M. A. 63:1473 (Oct. 24) 1914.

26. Brown, L. T.: Boston M. & S. J. 174:652, 1916.

27. Goldthwaite, quoted by Brown.[26]

28. Görres. H.: Deutsche med. Wchnschr. 47:897, 1921.

4. Benign tumors of the ribs or of the scapulae do not ordinarily produce scapular snapping, though Habermann [29] reported 2 cases, in 1 of which a chondroma and in the other of which an osteochondroma were found. Bloch [30] reported a case in which the nature of the tumor was not stated. No cases of malignant tumors have been reported as producing snap formation.

5. Other causes which have resulted in anomalous relationships of the bony structures with consequent sound production have been observed. Fracture of the scapula, producing a snapping easily audible at a distance of 9 feet (274.3 cm.), was reported by Favier.[31] Gaujot [32] reported a case in which a fracture of the scapula was followed by the formation of a large bursa. Terrillon reported a similar case in which a hygroma, containing rice bodies, developed under the scapula following a fracture of the ribs. Whether these cases are to be given absolute credence is doubtful, since they all occurred in the preroentgen era.

6. The association of snapping with angulation or buckling of the ribs, as is found in scoliosis, has been reported by Volkmann (2 cases) and Jacoby.

7. Trélat and Peré [33] reported cases in which the snapping was believed to be due to syphilis. In Trélat's case the voluminous subscapular tumor receded in size under antisyphilitic treatment. Galvagni reported 2 cases, Walther [5] 1 case and Lemoine [34] another case in which tuberculosis was considered the underlying etiologic factor. In these cases, either primary caries of the ribs, with or without cold abscess formation, or undue prominence of the ribs as a result of secondary deformity of the chest has been held responsible for the sound formation.

CHANGES IN THE MUSCULATURE

The second main group in which scapular crepitus has been noted is that associated with changes in the muscles lying between the scapula and the ribs. Here, too, a number of explanations have been suggested by different authors. Mention has already been made of the opinion of Jastram as to the significance of inflammatory changes in the muscles. Voelcker [35] suggested that a lesion in the muscle similar to tendonitis crepitans might be responsible for this type of snapping. The crepitus noted after operation in case 5 may in some respects be considered as substantiating this opinion. On the other hand, it must be admitted

29. Habermann, R.: Berl. klin. Wchnschr. **48**:612, 1911.

30. Bloch, O., quoted by Jacoby.[10]

31. Favier, H.: Gaz. d. hôp. **67**:1108, 1894.

32. Gaujot, quoted by Küttner; [20] quoted by Huguier.[17]

33. Peré: J. d. mal. cutan. et syph. **11**:133, 1899.

34. Lemoine, in discussion of Hendrix: J. de chir. et ann. Soc. belge de chir. **7**:120, 1907.

35. Voelcker, quoted by Volkmann.[18]

that it would be extremely difficult to prove this hypothesis unless widespread incision and examination were made at the time of operation. In most cases these measures are impossible, and simple microscopic changes of lesser degree, in our opinion, cannot be accepted as in any measure satisfactory evidence.

Ledentu,[36] Testut [37] and others have pointed out that not degenerative or inflammatory conditions, but rather anatomic variations of muscles, such as the anterior serratus, are to be held responsible for the production of sound. They have observed that not uncommonly fasciculi of the anterior serratus muscle may be wanting and that the interspace between the digitations may be covered by a thin connective tissue layer. As a consequence of this, sounds may be produced either by the snapping of the free edge of one of these digitations over the angle of the scapula, or by the rubbing of the uncovered scapula against the ribs at its inferior angle. Terrillon and Zaphiriadès each reported a case which they believed bore out the former of these two suggestions, but since no further details are given, the cases must be accepted with some reservation. Terrillon reported 3 other cases in which he believed the latter of the two hypotheses to be effective. The observations were made in 3 patients in whom, following ankylosis of the shoulder, a marked atrophy of the scapular muscles occurred. To this both Terrillon and Mauclaire, who reported a similar case, attributed the production of sound.

In regard to the former of these two hypothetic explanations, we are unable to express any opinion, but as to the latter, it may be doubted on purely a priori grounds. In the first place, it must be apparent that when ankylosis of the shoulder had occurred, hypertrophy rather than atrophy of the serratus would be expected. But even if atrophy were present, winging of the scapula, with a consequent absence of snap formation, as was shown in case 4, should be noted. In the second place, it would seem that with the relatively large number of ankyloses at the shoulder, produced either artificially or accidentally, some mention would have been made of the appearance of this phenomenon by other authors. Since snapping of the shoulder does not ordinarily occur following ankylosis of the shoulder, it is our opinion that forces other than those suggested must be at work.

CHANGES IN THE BURSAE

The third main group is that in which scapular snapping has been attributed to the presence of normal or adventitious bursae. Normally, two bursae are present beneath the scapula; the one at the upper angle

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36. Ledentu, quoted by Huguier.[17]

37. Testut, quoted by Ssoson-Jaroschewitsch, A. J.: Arch. f. klin. Chir. **123:** 378, 1923.

(bursa mucosa angulae superioris scapulae) is situated in the depths of the anterior serratus muscle, and is present about once in every 8 persons examined. The other, somewhat rarer (bursa mucosa serrata), is found in the connective tissue between the anterior serratus muscle and the upper part of the lateral wall of the chest.

Growth of these bursae, especially of the thick-walled, rice-filled variety, has been considered a factor in the production of scapular snapping. Camus [5] described such a case found at autopsy, as did Galvagni and others. Hendrix [38] reported a case in which he believed the sound was caused by an inflammation in one of the subscapular bursae, while Jacoby reported a case in which the x-ray picture showed two irregular shadows beneath the level of the scapular spine. These he considered to be calcium deposits in the bursa subscapularis. We have seen no similar case.

In the foregoing part the clinical characteristics of this condition have been sufficiently emphasized to require no further reiteration. To a large extent the therapy, too, has been indicated in its general outlines. It may, however, be advisable to review briefly the procedures which have been recommended in the treatment of this condition. Both surgical and nonsurgical procedures have been described. In general conservative measures have been of value only in those cases in which changes in the soft structures were suspected. Terrillon obviated the symptoms in one of his patients by the fashioning of a brace designed to limit the motion of the scapula without interfering with the function of the shoulder. In another case he drained the subscapular bursa, with subsequent infection and death. No autopsy was obtained. In some cases, simple counterirritation, as by vesication in the case reported by Galvagni, has given satisfactory results. In other cases physical therapy and massage have been of value. Mauclaire performed a muscle plastic, by reflecting a quadrangular flap of the rhomboids or of the trapezius and suturing it to the undersurface of the scapula, where it was presumed to act as a cushion, protecting against abnormal rubbing of the scapula against the wall of the chest. Though this procedure seems to have given satisfactory results in several cases, it has been criticized by others on the ground that the reflected muscle flap promptly deteriorated and was replaced by a thin, atrophic layer of connective tissue, which defeated the original purpose of the operation. Where there have been definitely demonstrable bony changes, an effort has been made to remove the cause of operation. In some cases the superior and in other cases the inferior angle of the scapula has been resected. In our case and in several others reported in the

38. Hendrix: J. de chir. et ann. Soc. belge de chir. 7:120, 1907.

literature the upper margin of the scapula was amputated, while in still others angulated portions of ribs or scapula were removed, with some success.

SUMMARY OF SNAPPING SCAPULA

An unusual syndrome has been described, the chief feature of which is the production of a snapping sound on motion of the scapula. The etiology is varied. For the most part, only conservative treatment need be instituted, but when there are definite bony changes, as, for example, excessive forward bending of the scapula and exostosis, surgical removal of the offending part should be undertaken.

HUMERUS VARUS

During the course of the roentgenographic examination in case 5 we were struck by the peculiar conformation of the head of both humeri. Figure 1 shows quite characteristically the extreme downward bending of the head of the humerus, analogous to the condition found more commonly in coxa vara. The head appeared in no way malformed, but the glenoid appeared to be definitely smaller than normal and to project outward like a nipple. The neck appeared markedly shorter and its angle with the head and shaft of the humerus much decreased. The plane of the anatomic neck, instead of being oblique, became almost vertical, and, on the left side, the level of the upper edge of the great tuberosity was definitely higher than the head of the humerus. There was no evidence, either clinically or roentgenologically, of any interference in the motions of the shoulder joint. Roentgen examination of other parts of the bony skeleton revealed no similar lesion, and we believe we are justified in excluding any systemic condition such as rachitis or achondroplasia.

This condition has been called humerus varus and was first described by Riedinger[39] in 1900. Since then a number of articles on the subject have appeared in the Swiss and Italian literature, but nothing at all as yet in the English literature. Humerus varus in general is characterized by a high position of both the great tuberosities in relation to the head of the humerus, by a diminution in the radius of the curvature of the humerus, by a change in the angle of the neck, by a shallowness in the depression normally found between the head and the anatomic neck of the humerus and by the more vertical position of the anatomic neck of the humerus. In the few cases which have been examined pathologically (Bircher), the humerus showed an absence of its normal structure, the spongiosa being narrow and irregular, and the marrow presenting a peculiar foamy consistency.

.39. Riedinger, J.: Deutsche Ztschr. f. Chir. **54**:565, 1900; Kongr. d. deutsch. Gesellsch. f. orthop. Chir. **3**:317, 1909.

Nicotra,[40] whose article presents an excellent bibliography on the subject, divided humerus varus into two groups, false humerus varus and true humerus varus.

False humerus varus may be due to a number of factors, such as fracture of the anatomic or surgical neck of the humerus. Some have considered that this type should be characterized by a special designation, such as humerus varus adductus. Other cases have been reported in which humerus varus has been noted in arthritis and in tumor formation, with consequent malacia of the bone, and Riedinger reported a case in which a humerus varus of 100 degrees was found in a case of ankylosis of the elbow. This varus development Riedinger considered as being an adaptive mechanism to accommodate for the ankylosis of the elbow. In general, this type of varus causes an interference with motion of the shoulder joint, compatible with its underlying pathologic changes. Little attention has been focused on it.

Nicotra has subdivided true humerus varus into two main types: humerus varus dystrophicus and humerus varus adolescentium (cysticum). In the former, or dystrophic, group may be placed the type of varus seen in rickets (Riedinger), in cretinism and in chondrodystrophy (Bircher). In these cases the varus deformity is, of course, secondary to general dystrophic changes in the skeleton. Bircher [41] has described several anatomic specimens obtained from cretins, in which he noted flattening of the head, a reduction in the angle of inclination of the neck of between 20 and 40 degrees, a decrease in the directional angle of the neck of the humerus, a decrease in the radius of the curvature of the head, an elevation of both greater and lesser tuberosities of the humerus and an inward torsion of the upper part of the shaft of the humerus. No characteristic changes have been noted in the glenoid cavity, though in 1 case Haumann [42] described changes similar to those seen in epiphysitis. The muscular insertions, especially the cristae of the intertuberculous sulcus, are prominently developed. The changes observed in the cretin have also been seen in microcephalic dwarfs, in achondroplasia and, occasionally, it has been said, in rickets. Some have considered the changes as a reversion to type, such as is usually seen in anthropoid apes and in human embryos. Bircher has attributed them to the general dystrophic changes with late walking and consequently prolonged creeping during infancy. As a result of this, the weight of the trunk on the arms and the excessive pull of the deltoid have been thought to lead to humerus varus. The condition is symptomless, produces no limitation of motion, gives no discrepancy in the relative length of the arm and requires no treatment.

40. Nicotra, A.: Clin. chir. **33**:914, 1930.
41. Bircher, E.: Deutsche Ztschr. f. Chir. **96**:598, 1908; Fortschr. a. d. Geb. d. Röntgenstrahlen **16**:325, 1911.
42. Haumann, W.: Beitr. z. klin. Chir. **140**:136, 1927.

Humerus varus adolescentium (cysticum), on the other hand, is an unusual clinical entity, originally described by Stropeni[43] and subsequently by Nicotra. It usually occurs in the second decade of life and is characterized by apparent subluxation of the head. There is definite limitation of abduction, with shortening of the arm, even up to 8 or 10 cm. Pain may or may not be present. The x-ray pictures are distinctive, and since no pathologic material is at hand, they afford the only means of etiologic interpretation. The varus occurs in the surgical neck, at the junction of the metaphysis and diaphysis. The epiphyseal line may show early consolidation. The diaphysis at its uppermost part is much thinned and usually contains on its medial aspect what is interpreted as a solitary cyst, through which pathologic fracture may occur. The head of the humerus, slightly reduced in size, but otherwise normal, fits within the deepened groove or depression (insaccatura) made by the cyst. There is a displacement of both tuberosities upward, with a marked decrease in the angle of inclination, even up to 50 degrees. To a lesser extent there is a change in the directional angle, but torsion of the humerus is not evident.

Nicotra noted that humerus varus adolescentium is observed only in cases of this solitary type of cyst, and never in cases of multiple cysts of the humerus. The explanation adduced by Nicotra is ingenious; it still needs confirmation. Seiffert,[44] on the other hand, described a case which falls in this group, but he attributed it to a questionable injury sustained at birth.

The number of cases thus far described is small, not more than 11 having been noted. Except when there is a definite limit of abduction at the shoulder, no treatment is necessary. Anglesio[45] is the only one who until now has attempted osteotomy of the upper part of the humerus for the purpose of correction of the varus deformity.

The case which we reported (case 5) does not seem to fit into any of the classifications previously mentioned, and we have the feeling that it belongs in the group which may be termed congenital humerus varus. Such a classification has previously been suggested, but no case has heretofore been described. We have no doubt that were closer attention to be paid to the variation in the angle of the neck of the humerus, numerous similar cases might be brought to light. Since practically the only means of diagnosis in these cases is by the x-rays, some attention should be paid to the technic of taking x-ray pictures. Köhler[46] noted that in the prone position varus of the humerus may be simulated, even in the normal arm. For the purpose of obviating these difficulties,

43. Stropeni, L.: Chir. d. org. di movimento **12**:531, 1928.
44. Seiffert, J. L.: Fortschr. a. d. Geb. d. Röntgenstrahlen **43**:620, 1931.
45. Anglesio, B.: Arch. di ortop. **46**:417, 1930.
46. Köhler, Alban: Röntgenology, translated from the German by Arthur Turnbull, New York, William Wood & Company, 1928, p. 72.

Preisser[47] suggested that the x-ray picture be taken with the arm externally rotated and somewhat abducted. No treatment is, of course, necessary in this type of case, since usually no symptoms exist.

ADDENDUM

We have recently been fortunate in being able to reexamine a patient suffering from Gaucher's disease in whom marked changes in the skeletal system were observed. Since this is the first, if not the only, case in which a humerus varus has been observed in Gaucher's splenomegaly, we feel justified in briefly presenting the x-ray photographs taken in this case.

Fig. 4.—*A*, roentgenogram taken in 1927; *B*, one taken in 1932.

A fairly complete discussion of the bone changes was previously published,[48] and the reader is referred to that article for the more intimate details of the patient's condition. For purposes of comparison, the x-ray photograph of the findings observed in the right shoulder in 1927 is herewith reproduced (fig. 4 *A*). Apart from the characteristically mottled appearance of the bone, it will be observed that the angle of the neck of the humerus is quite normal. If the x-ray photograph of the patient's shoulder made in 1932 is examined (fig. 4 *B*), it will be seen that the angle of the neck is markedly decreased, so that this patient has a true humerus varus.

47. Preisser, G.: Fortschr. a. d. Geb. d. Röntgenstrahlen **12**:3, 1908.

48. Milch, H., and Pomeranz, M.: Bone Changes in Gaucher's Splenomegaly, Ann. Surg. **89**:552 (April) 1929.

As was previously noted, Bircher attributed the development of humerus varus in the rachitic cases which he examined to a prolonged period of creeping. However, in this case this factor can be completely eliminated as part of the causative mechanism of the humerus varus. It must be presumed, then, that the distorting forces are to be found in the muscles of the shoulder joint acting on a neck in which the normal tensile strength had been reduced as a result of the displacement of osseous tissue by an infiltration of Gaucher's cells.

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EFFECTS OF CHOLECYSTECTOMY ON THE BILIARY SYSTEM

A MORPHOLOGIC STUDY IN THE DOG

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Opinions still differ regarding the effects of surgical removal of the gallbladder on the rest of the biliary system. The clinical importance of this matter urged us to a reinvestigation. It soon became evident, however, that the problem was too complex to be considered as a whole, and for that reason we chose to confine our investigation in the dog to merely one phase, namely, the morphologic.

In reviewing the literature, we learned that cholecystectomy is an operation three hundred years old. It was first performed on a dog in 1630 by the Italian Zambeccari. The first cholecystectomy on man was performed by Langenbuch [1] in the "Lazaruskrankenhaus" of Berlin on July 15, 1882. The history of cholecystectomy is vividly presented, and the views regarding the effects of such a procedure are critically reviewed in Rost's [2] paper of 1913. The problem has since been approached experimentally by a number of investigators, notably by

1. Langenbuch, C.: Chirurgie der Leber und Gallenblase, Stuttgart, Ferdinand Enke, 1894 and 1897.

2. Rost, F.: Die funktionelle Bedeutung der Gallenblase: Experimentelle und anatomische Untersuchungen nach Cholecystectomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 26:710, 1913.

Lapenta,[3] Judd and Mann,[4] Eisendrath and Dunlavy,[5] Hartman, Smyth and Wood,[6] Gohrbandt,[7] Mairano,[8] Canavero,[9] Troitzky [10] and Sutton.[11]

Lapenta (1916) made a gross examination of the extrahepatic biliary system of "about" ten dogs, from twenty to sixty days following cholecystectomy. The extrahepatic biliary ducts were dilated in all his animals. In two the cystic stump dilated "in a bulb fashion."

Judd and Mann (1917) studied the effects of cholecystectomy on the dog (also on the cat and the goat). Their conclusions, however, that "after removal of the gallbladder all of the ducts outside the liver dilate" and that "the sphincter at the entrance of the common bile duct into the duodenum is the chief factor in producing this dilatation" are not convincingly supported by morphologic evidence.

Eisendrath and Dunlavy (1918) investigated the fate of the cystic duct following removal of the gallbladder in a number of dogs opened from one week to six months after cholecystectomy. They noted a progressive dilatation of the cystic duct.

Hartman, Smyth and Wood (1922) cholecystectomized nine dogs. In eight of these they retained from 6 to 20 mm. of the cystic duct, and in one none. The animals were reopened from six to fourteen weeks later. The extrahepatic biliary ducts were somewhat dilated in all; the cystic stumps, when retained, dilated to 1 cm. in diameter and elongated to from 1.2 to 2.5 cm. The microscopic structure of these stumps resembled that of a gallbladder and showed no evidence of thinning or stretching.

Gohrbandt (1927) experimented on dogs, removing the whole of the cystic duct at cholecystectomy in one series, retaining it in another, and retaining also the neck of the gallbladder in a third. In the first

3. Lapenta, V. A.: Is the Gallbladder a Useless and Functionless Organ? Interstate M. J. **23**:993, 1916.

4. Judd, E. S., and Mann, F. C.: The Effect of Removal of the Gall-Bladder, Surg., Gynec. & Obst. **24**:437, 1917.

5. Eisendrath, D. N., and Dunlavy, H. C.: The Fate of the Cystic Duct After Cholecystectomy: An Experimental Study, Surg., Gynec. & Obst. **26**:110, 1918.

6. Hartman, F. L.; Smyth, C. M., Jr., and Wood, J. K. W.: The Results of High Ligation of the Cystic Duct in Cholecystectomy, Ann. Surg. **75**:203, 1922.

7. Gohrbandt, E.: Gibt es eine Neubildung der Gallenblase? Arch. f. klin. Chir. **145**:286, 1927.

8. Mairano, Mario: Le modificazioni delle vie biliari dopo la colecisectomia, Arch. ital. di chir. **20**:468, 1928.

9. Canavero, Michelangelo: L'influenza della colecistectomia sulle vie biliari, Policlinico (sez. chir.) **35**:429, 1928.

10. Troitzky, A. A.: Changes in Liver and Biliary Tract After Excision of Gallbladder, Omsky med. j. **4**:21, 1929.

11. Sutton, J. E., Jr.: Changes in the Intrahepatic Bile Ducts Following Cholecystectomy, Ann. Surg. **91**:65, 1930; abstr., Arch. Path. **9**:764 (March) 1930.

series of four dogs, reexamined one, two, three and four months following the operation, no regeneration of the cystic duct occurred, nor was there any dilatation at its site. In his second series of four animals, a bulblike distention of the retained cystic duct was noted one, two, three, four and five months following the operation. The microscopic structure of the stump was that of a dilated cystic duct and not that of a gallbladder. In three additional dogs the same procedure was repeated, and with the idea of injuring the cystic stump the peritoneal covering of the cystic duct was stripped. In these animals a more marked dilatation of the cystic duct occurred than in the previous series. The distention stopped at the junction of the cystic duct and the ductus choledochus. In five dogs, in which the resected end of the cystic duct was properly cared for, i. e., the peritoneum was closed over the stump, no dilatation of the cystic duct occurred. In three dogs of the third series, a small portion of the gallbladder was retained together with the cystic duct. These, when examined two, four and six months, respectively, following the cholecystectomy, showed a gallbladder about half the size of the original. No mention is made by Gohrbandt of any dilatation of the hepatic and common bile ducts following these procedures.

Mairano (1928) studied the biliary system of seven dogs, 12, 40, 90, 120, 150, 240 and 390 days following cholecystectomy. He observed dilatation of the extrahepatic biliary ducts in all of his animals, illustrating his findings with roentgenograms. The cystic duct, retained in two of his dogs, revealed normal microscopic structure in spite of the gross enlargement.

Canavero (1928) made morphologic studies on the biliary system of eight dogs from fifteen days to fifteen months following cholecystectomy. In his first group of two animals, no significant gross or microscopic changes were noted in the extrahepatic or intrahepatic biliary ducts fifteen days following removal of the gallbladder. In his second group of three animals, thirty-five, sixty and ninety-six days following cholecystectomy, dilatation of the extrahepatic biliary ducts occurred with an increase in size of the cystic stump. The microscopic changes described were neither definite nor characteristic. The morphologic changes in the third group of three animals, ten, fourteen and sixteen months following cholecystectomy, were about the same as in the second group. Canavero concluded from these experiments that the changes in the biliary system occur within one month following removal of the gallbladder.

Troitzky (1929) removed the gallbladders of seven dogs. Microscopic examination of the liver four months following the operation

showed a chronic inflammation. The extrahepatic biliary ducts were dilated. There was no evidence of a tendency to the formation of a new gallbladder.

Sutton (1930) removed the gallbladders of eighteen dogs. From fifteen to seventy-seven days after this cholecystectomy he injected a 12 per cent solution of silver gelatin through the common bile duct under a pressure of from 100 to 180 mm. of mercury and placed the specimens in an ice-cold 5 per cent solution of formaldehyde. The same procedure of injection and fixation was carried out in six normal dogs. Subsequent microscopic studies showed that in the control ani-

Effects of Cholecystectomy on the Extrahepatic Biliary Ducts of the Dog

Dog	Sex	Weight, Kg.	Duration of Experiment, Weeks	Appearance of Extrahepatic Biliary Ducts at Close of Experiment		
				Gross	Microscopic	Cystic Stump
C-13	♀	16	1	Normal	Normal	Not dilated
C-14	♀	8	1	Normal	Normal	
C-7	♂	8	2	Normal	Normal	Not dilated
C-8	♂	10	2	Dilated	Dilated	Not dilated
C-10	♂	12	3	Dilated	Dilated	
C-9	♂	17	4	Normal	Normal	Not dilated
C-16	♂	8	4	Normal	Normal	Not dilated
C-11	♂	13	5	Normal	Normal	Not dilated
C-12	♂	10	5	Dilated	Normal	
C-17	♂	9	6	Dilated	Dilated	Dilated
C-18	♂	8	6	Normal	Normal	Not dilated
C-19	♀	9	8	Normal	Normal	Not dilated
C-20	♂	10	8	Normal	Normal	Not dilated
C-5	♀	8	10	Normal	Normal	Not dilated
C-6	♂	14	10	Dilated	Dilated	Not dilated
C-4	♀	13	11	Dilated	Normal	Not dilated
C-3	♂	16	12	Dilated	Normal	Not dilated
C-21	♀	9	12	Dilated	Normal	Not dilated
C-1	♂	10	16	Normal	Normal	Not dilated
C-22	♂	12	16	Dilated	Dilated	
C-23	♀	7	20	Dilated	Dilated	Dilated
C-24	♂	10	20	Dilated	Dilated	Dilated
C-25	♂	9	23	Dilated	Dilated	Not dilated
C-26	♂	10	23	Dilated	Dilated	Dilated

mals a cuboidal epithelium lined the intrahepatic biliary ducts and a high columnar epithelium the mucosa of the gallbladder. Fifteen days following the removal of the gallbladder, in the intrahepatic biliary ducts, "the surface of the epithelium was irregular; new cells projected into the lumen," and "there was apparent bud formation." From forty to seventy-seven days following cholecystectomy, "numerous mucous folds and villi of varying sizes were seen projecting into the lumen of the ducts," and a "change of the epithelial cells from the cuboidal type, with no real resemblance to the gallbladder cells, to high columnar cells" which "approached the morphologic appearance of the epithelial cells of the gallbladder" occurred.

Our investigations were concerned with the morphologic appearance, gross and microscopic, of the biliary system of the dog subsequent to surgical removal of the gallbladder.

Fig. 1.—The extrahepatic biliary ducts of a dog (C-5) ten weeks following cholecystectomy. No gross or microscopic evidence of dilatation of the ducts was noted.

Fig. 2.—Marked dilatation of the extrahepatic biliary ducts of a dog (C-6) ten weeks following cholecystectomy. Although the extrahepatic biliary ducts were markedly dilated grossly and also microscopically, no pertinent changes were noted in the intrahepatic ducts and in the parenchyma of the liver (see fig. 3).

METHOD

From twenty-four apparently healthy dogs, weighing between 7 and 17 Kg., the gallbladders were removed by dividing the cystic duct as close to the ductus choledochus as was practicable. Subsequently the gallbladders were examined grossly and microscopically. The condition of the liver and the extrahepatic biliary ducts was noted at the time of removal of the gallbladder. From one to twenty-three weeks following the cholecystectomy a second laparotomy was performed, and the gross appearance of the liver and the extrahepatic biliary ducts again noted; then the entire system was removed and fixed *in toto*. Subsequently, the whole of the extrahepatic biliary ducts was divided into blocks of from 1 to 2 cm. in length and embedded in celloidin. In each case, sections were prepared from
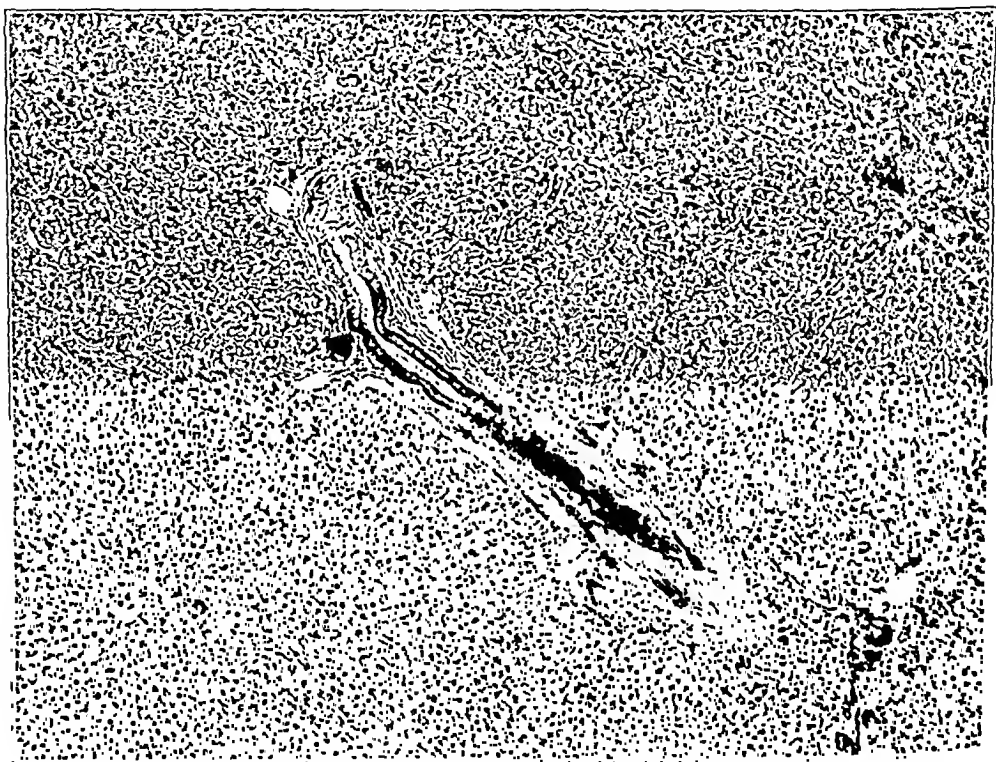
Fig. 3.—Section of the liver of a dog (C-6) ten weeks following cholecystectomy; × 85. Although the extrahepatic biliary ducts show marked dilatation (see fig. 2), gross and microscopic, no pertinent changes are noted in the parenchyma of the liver. A medium-sized intrahepatic duct seen in longitudinal section is not dilated; its lumen is lined with tall columnar epithelium; there are no signs of budding or epithelial proliferation.

every block and from portions of various parts of the liver and stained with hematoxylin-eosin and iron-hematoxylin and by the method of van Gieson.

MORPHOLOGIC OBSERVATIONS

In all of the twenty-four dogs used in these experiments, the biliary system appeared normal grossly at the time of the cholecystectomy and the gallbladders removed showed no gross or microscopic changes.

First Group.—In this group of eleven dogs, the biliary systems were removed between the first and sixth week following the cholecystectomy (table). The extrahepatic biliary ducts appeared grossly distended at the close of the experiment in four of the eleven dogs. Microscopically, however, in only three were the folds of the mucosa low or missing and the lining epithelium flattened in places. In none of the remaining eight dogs was there any microscopic evidence of undue dilatation of the ducts, for in all the mucosa was thrown into folds and lined by a
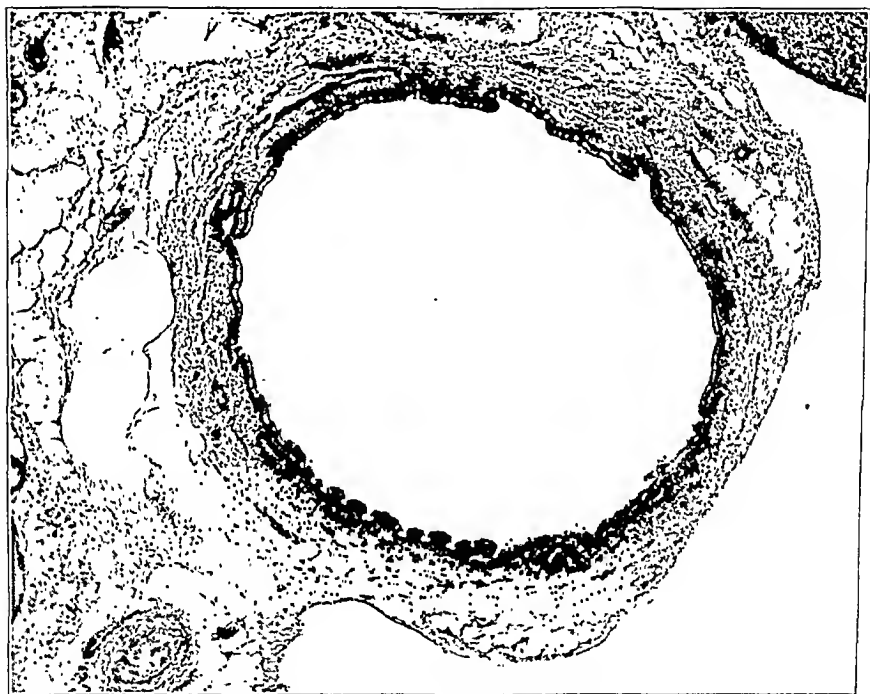
Fig. 4.—Section of a small hepatic duct at the porta hepatis of a dog (C-26) twenty-three weeks following cholecystectomy; × 45. The tall columnar epithelium lining the lumen is flattened, the folds of the mucosa are few and low, and the indentations are shallow.

single row of tall columnar epithelium. No pertinent changes were noted in the parenchyma of the liver or in the intrahepatic biliary ducts.

Second Group.—In this group of seven dogs, the biliary systems were removed between the eighth and twelfth week following the cholecystectomy (table). The extrahepatic biliary ducts appeared grossly distended at the close of the experiment in four of the seven dogs, only one of which, however, exhibited microscopic evidence of a dilatation such as lowering or absence of the folds of the mucosa and occa-
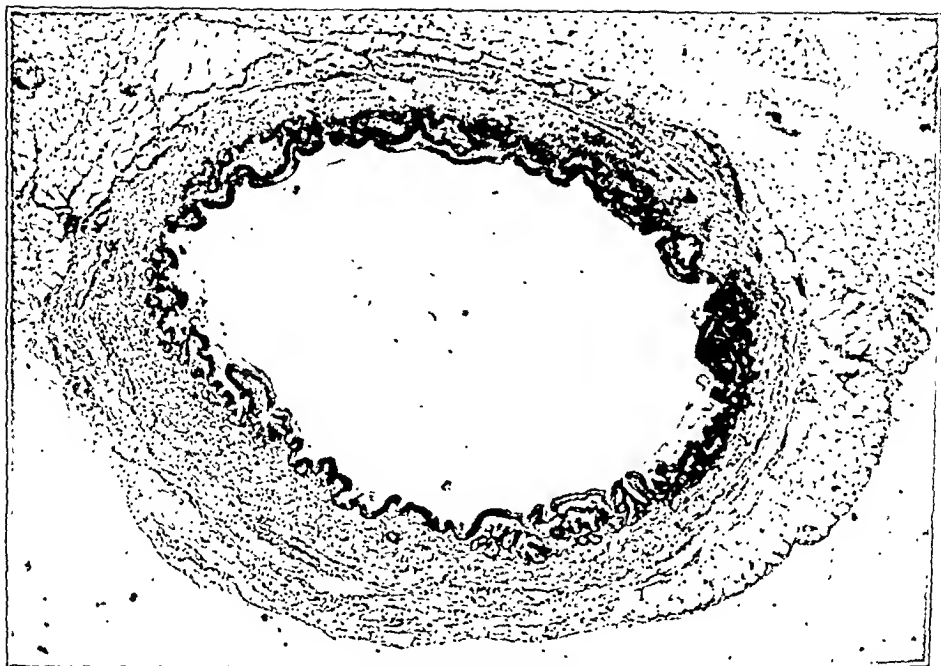
Fig. 5.—Cross-section of the ductus choledochus of a dog (C-7) from near the junction of the cystic and hepatic ducts two weeks following cholecystectomy; × 25. There is no evidence of dilatation of the duct: The lumen is well shaped and lined with a single row of tall columnar epithelium; folds project into the lumen; indentations of the mucosa are frequent. Epithelial-lined lumina in the wall are numerous.
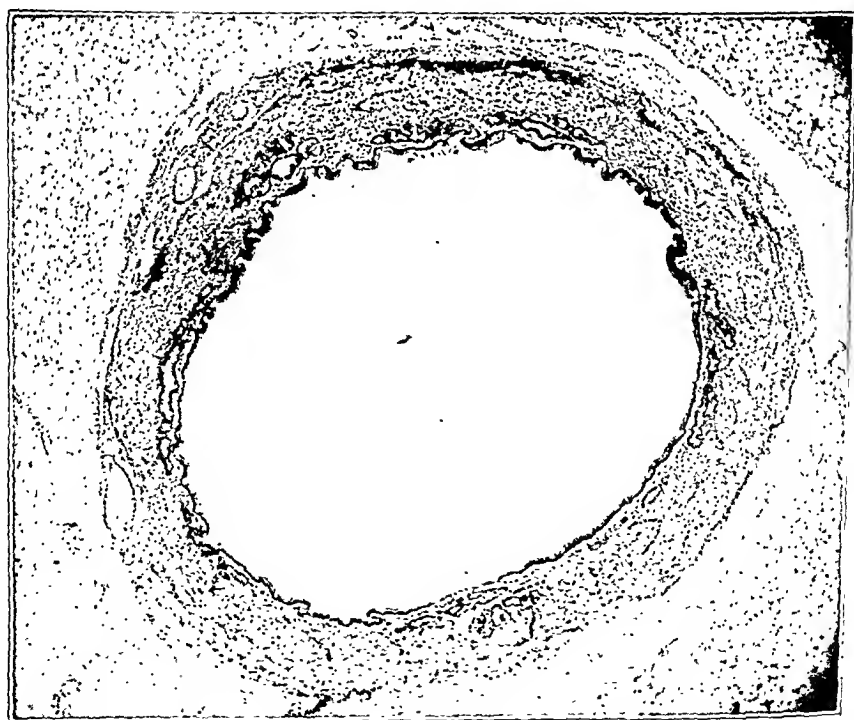
Fig. 6.—Cross-section of the ductus choledochus of a dog (C-8) two weeks following cholecystectomy; × 25. There is marked dilatation of the ductus choledochus: The lining epithelium is flattened in places; the folds of the mucosa are low or absent; the indentations are shallow. Epithelial-lined lumina in the wall are frequent.

sional flattening of the lining epithelium. No changes were noted in the parenchyma of the liver or in the intrahepatic biliary ducts (figs. 1 to 3).

Third Group.—In this group of six dogs, the biliary systems were removed between the sixteenth and twenty-third week following cholecystectomy. In all but one of these animals the extrahepatic biliary ducts appeared grossly distended at the close of the experiment and exhibited some microscopic evidence of dilatation. The parenchyma of the liver and the intrahepatic biliary ducts disclosed no pertinent microscopic changes.
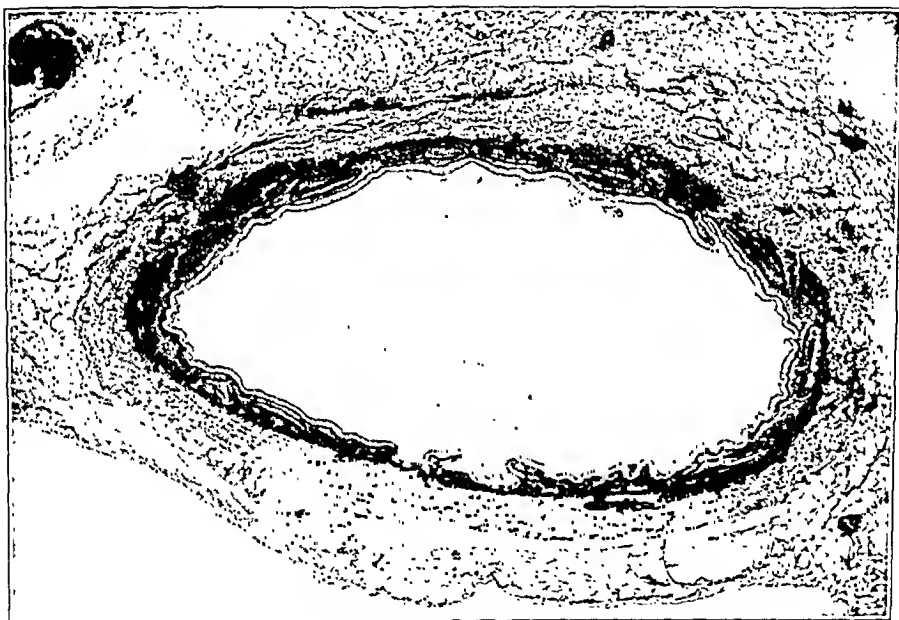
Fig. 7.—Cross-section of the ductus choledochus of a dog (C-25) just proximal to its intramural portion twenty-three weeks following cholecystectomy; × 25. The absence of muscle fibers in the wall of the ductus choledochus is conspicuous. The folds of the mucosa are few, the indentations shallow. Numerous epithelial-lined lumina are seen in the mucosa, but no glands. The lining epithelium is tall, columnar and slightly flattened in places.

It should be restated that in none of the twenty-four dogs were there any pertinent changes in the parenchyma of the liver or gross or microscopic evidence of a dilatation of the intrahepatic biliary ducts following cholecystectomy (fig. 3). The lumina of the small and middle-sized biliary ducts were open and lined by a single row of low columnar epithelium. While the mucosa of these ducts was void of folds, the large intrahepatic ducts showed slight elevations and shallow indentations of the mucosa.
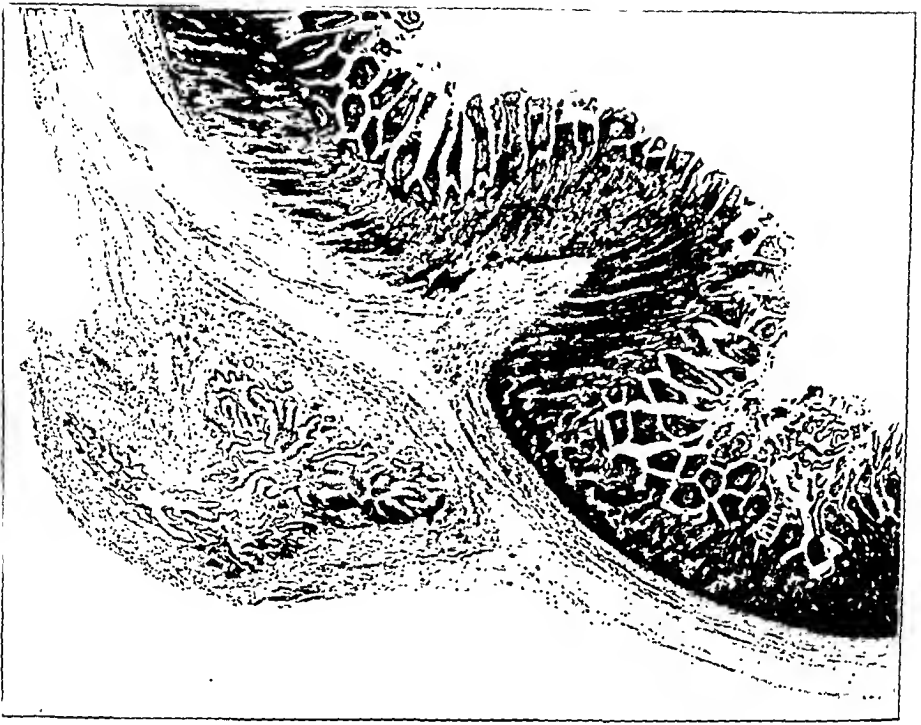
Fig. 8.—Cross-section of the intramural portion of the ductus choledochus of a dog (C-26) twenty-three weeks following cholecystectomy; × 14. The longitudinal layer of the muscular coat of the duodenum is seen to be split in order to admit the ductus choledochus. No muscle fibers are seen in the wall of the duct opposite the duodenum.
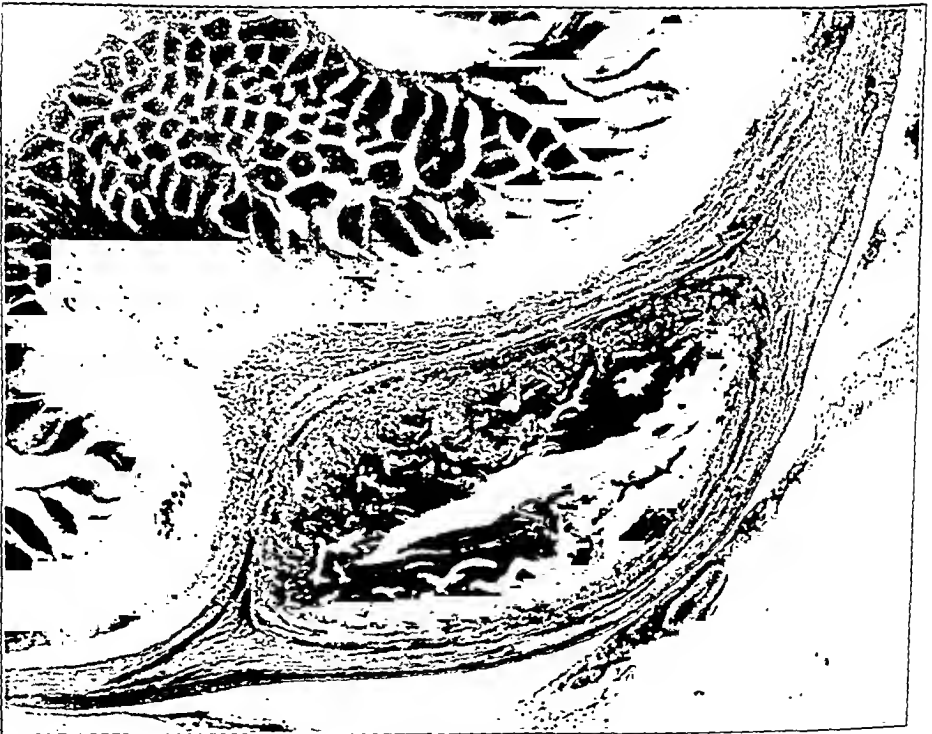
Fig. 9.—Terminal end of the ductus choledochus of a dog (C-25) twenty-three weeks following cholecystectomy; × 14. The duct is seen passing through the circular layer of the muscular coat of the duodenum. The isolated muscle bundles scattered about the external layer of the wall of the ductus choledochus appear to be part of the circular layer of the duodenal wall, the muscle bundles of which have separated and changed their course in order to admit the duct.

Of the extrahepatic biliary ducts, particular attention was paid to the cystic stump, of which sections were obtained in twenty of the twenty-four dogs. In only four of these was there any definite evidence of dilatation (table). Such changes were always associated with dilatation of the rest of the extrahepatic biliary ducts and did not occur without such.

In all the extrahepatic biliary ducts there were frequent outpouchings of the mucosa toward the external layers (fig. 5). Occasionally some of these outpouchings appeared as round or oblong lumina lined by a single row of low columnar epithelium the cells of which had a

Fig. 10.—Section through the papilla of Vater of a dog (C-7) two weeks following cholecystectomy; × 14. The lumen of the ductus choledochus is seen to merge with the lumen of the duodenum. The muscle fibers in the wall of the duct are scanty and irregularly distributed.

lightly staining cytoplasm and a flat nucleus; apparently they were mucous glands. The number of the epithelial-lined lumina in the wall of the ducts varied considerably in different dogs and in various parts of the tract of the same dog. No increase in size or number of these outpouchings or of the folds was noted in the series examined, nor was there any evidence of budding of the folds or proliferation of the surface epithelium. External to the thin tunica propria mucosae the wall of the medium-sized and large intrahepatic and also the extra-

hepatic biliary ducts was seen to be composed of a dense layer of connective tissue rich in fibers arranged more or less circularly.

The wall of all the biliary ducts was noted to be void of muscle fibers (figs. 4 to 7). In the wall of the terminal portion of the ductus choledochus scattered bundles of muscle fibers were noted occasionally, but not until the duct had actually reached the duodenum (figs. 8 to 10). The course and arrangement of the muscle bundles in sections across the intramural portion of the ductus choledochus left some doubt as to the existence of an anatomic sphincter of Oddi in the dog.

<div align="center">COMMENT</div>

The effects of the cholecystectomy, it seems, must primarily depend on the preoperative working condition of the biliary system and also on individual anatomic variations regarding the arrangement of the ducts. For this reason we eliminated from our series dogs the livers of which appeared grossly damaged or the gallbladders of which were not grossly and microscopically normal. At present too little is known of the anatomic variations in the arrangement of the biliary ducts to be of use in interpreting the effects of surgical removal of the gallbladder of the dog. While it seems logical to attribute a great deal of importance to the mechanism regulating the flow of bile into the duodenum, it must be admitted that no exact knowledge is at hand about this function.[12] Our morphologic observations on the intramural portion of the ductus choledochus, which will be presented in detail elsewhere, leave us in serious doubt as to the existence of an anatomic sphincter of Oddi in the dog. This again helps to confuse rather than to explain the situation.

In a preliminary report we presented data on twelve dogs the biliary systems of which were studied morphologically from two to sixteen weeks after cholecystectomy.[13] The results obtained in this group of animals seemed to warrant the conclusion that "dilatation of the extrahepatic biliary ducts, if it occurs, is independent of the time elapsing after removal of the gallbladder." However, the present final report on twenty-four dogs the biliary systems of which were studied from one to twenty-three weeks following cholecystectomy does not support this contention. Of eighteen dogs studied between the first and twelfth weeks following cholecystectomy, only four (22.2 per cent) showed microscopic evidence of a dilatation, while identical changes were noted in five of six dogs (83.3 per cent) the biliary systems of which were

12. Halpert, Béla: The Gallbladder: Its Functions and Some of Their Disturbances in the Light of Recent Investigations, Arch. Surg. **19**:1037 (Dec.) 1929.

13. Healey, Claire; Rewbridge, A. G., and Halpert, Béla: Effects of Cholecystectomy on the Biliary System, Arch. Path. **9**:1295 (June) 1930.

studied between the sixteenth and twenty-third weeks after cholecystectomy. Our present final studies thus indicate that the extrahepatic biliary ducts may dilate at any time subsequent to cholecystectomy and that microscopic evidence of dilatation develops about four times more frequently between the fourth and sixth months than in the first twelve weeks after removal of the gallbladder.

SUMMARY AND CONCLUSIONS

The gallbladders of twenty-four apparently healthy dogs were removed and with the rest of the biliary systems were studied morphologically from one to twenty-three weeks following cholecystectomy. The results obtained suggest the following: (*a*) The parenchyma of the liver and the intrahepatic biliary ducts suffer no pertinent changes in the first six months following surgical removal of the normal gallbladder. (*b*) The extrahepatic biliary ducts may dilate at any time subsequent to cholecystectomy; microscopic evidence of dilatation develops about four times more frequently between the fourth and sixth months than in the first twelve weeks following removal of the gallbladder.

The variable effects of cholecystectomy on the extrahepatic biliary ducts may be dependent on the preoperative working condition of the biliary system, on individual anatomic variations of the structure and the arrangement of the ducts and, finally, on the mechanism regulating the flow of bile into the duodenum.

A study of the intramural portion of the ductus choledochus, in the present series of animals, casts serious doubt as to the existence of an anatomic sphincter of Oddi in the dog.

LYMPH VESSELS IN RABBIT CARCINOMA

WITH A NOTE ON THE NORMAL LYMPH VESSEL STRUCTURE OF THE TESTIS

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AND

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BALTIMORE

In 1908, Evans[1] published a short article on the occurrence of newly formed lymphatic vessels in malignant growths. In this paper he stated that important publications and books of reference, such as those of Borst,[2] Ribbert, Ziegler, Lubarsch-Ostertag and Thoma, failed to report "any instance in which proper lymphatic vessels were found growing in malignant tissue." In fact, that statement holds good today, because examination of more recently published volumes, such as the exhaustive work of Ewing[3] on neoplastic diseases, and of the textbooks of Aschoff,[4] Karsner,[5] Sternberg[6] and Adami,[7] has showed that they have nothing to add to the previous works on this subject. The textbook of MacCallum,[8] however, is an exception, because here it is stated that as a result of the injection experiments of Evans, it is known that lymphatics are abundantly present in human tumors. This work of Evans will be discussed later. Another exception is the textbook of McFarland,[9] in which it is stated that "lymphatics of neoplasms are

1. Evans, H. M.: On the Occurrence of Newly-Formed Lymphatic Vessels in Malignant Growths, with a Demonstration of Their Origin and Ingrowth in the Metastases of a Round Cell Sarcoma, Bull. Johns Hopkins Hosp. **19**:232, 1908.

2. Borst, Max: Die Lehre von den Geschwülsten, Wiesbaden, J. F. Bergmann, 1902.

3. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

4. Aschoff, L.: Pathologische Anatomie, Jena, G. Fischer, 1919.

5. Karsner, H. T.: Human Pathology, Philadelphia, J. B. Lippincott Company, 1929.

6. Sternberg, C.: Lehrbuch der allgemeinen Pathologie und der pathologischen Anatomie, begründet von H. Ribbert, Leipzig, F. C. W. Vogel, 1928.

7. Adami, J. G.: The Principles of Pathology, ed. 2, Philadelphia, Lea & Febiger, 1910.

8. MacCallum, W. G.: A Text-Book of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928.

9. McFarland, J.: A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1904.

usually plentiful, often superabundant, and may be plexiform or cavernous." This unsupported statement stands, therefore, in marked contrast to the conclusions of other writers on this subject. For the present it will suffice to say that in the course of some work [10] on the vital staining of rabbit carcinoma, the occasion presented itself to study the relationship between the lymph vessels of the normal testis and of the carcinoma which had been transplanted into the testicle.

MATERIAL AND METHODS

Ten rabbits that had been inoculated intratesticularly with cancer were used for the injections. All the animals were about 6 months old. It was soon found, from preliminary injections into other animals with cancer, that injections could be made into the lymphatics on the surface of the testis at almost any time, but that the process became more difficult with the increased age of the growth. Apparently, as the transverse diameter of the testis increased, the peritoneal covering, which forms the visceral layer of· the tunica vaginalis propria, also enlarged and kept pace with the tumor growth with the one important difference, as far as the lymphatics were concerned, that the tunica vaginalis was thinner and its lymph vessels were fewer, smaller and it was more difficult to make injections into them. The best specimens were obtained from those that had a tumor growth varying from 13 to 24 days of age. In four of the animals the lymph drainage was obstructed for three hours before the injections were made in order to distend the lymphatic system and thus obtain a more complete injection. The idea of distending lymph vessels to facilitate their injection has been of service in filling the lymph vessels of the liver (Lee [11]), gallbladder (Winkenwerder [12]), and thyroid (Rienhoff [13]). It happened, however, that one of the best injections of the parenchymatous lymphatics (figs. 4 to 6) was one in which the lymph vessels had not been previously obstructed.

India ink or a saturated solution of berlin blue was used for injection. By means of an ordinary syringe equipped with a 27 gage needle these substances were readily injected into the lymph vessels in the tunica vaginalis by direct puncture. This method was not only simple but also accurate, because to any one familiar with the injection of lymphatics there was no possible confusion of the lymph vessel pattern

10. Tilghman, R. C., and Lee, F. C.: The Vital Staining of Rabbit Carcinoma, Bull. Johns Hopkins Hosp. **49**:360, 1931.

11. Lee, F. C.: On the Lymph Vessels of the Liver, Contrib Embryol. **15**:63, 1923.

12. Winkenwerder, W. L.: A Study of the Lymphatics of the Gall-Bladder of the Cat. Bull. Johns Hopkins Hosp. **41**:226, 1927.

13. Rienhoff, W. F., Jr.: The Lymphatic Vessels of the Thyroid Gland in the Dog and in Man. Arch. Surg. **23**:483 (Nov.) 1931

with that of any other vascular system. The entire superficial lymphatic plexus would immediately fill and drain along large lymph vessels in the mesorchium. These vessels were at once recognized by the presence of numerous valves along their course. In five of the animals injections were also made into the blood vessels in order to check the effect of injection into the lymph system, but the lymph vessel pattern was so definite that in one half of the animals the vascular injection was omitted in order to make the study of the lymph system less complicated. · All the material was fixed in solution of formaldehyde. Some of the tissue was cleared in methylsalicylate, while other portions were sectioned as a routine procedure and stained with hematoxylin and eosin.

Fig. 1.—For orientation. Testis of a rabbit with extensive cancer growth twenty days after inoculation. India ink was injected into the lymphatics on the surface at one area, but they did not extend into the small white cancer mass situated in the middle of the area into which injection was made. This small cancer nodule is enlarged in figure 2. Natural size.

From all the material thus obtained three specimens were chosen to illustrate the relationship between the cancer growth and the lymph vessels.

One of these specimens was derived from a rabbit each testis of which had been inoculated with a suspension of rabbit carcinoma in salt solution. Twenty days later the animal showed marked loss of weight, was dragging its left leg, and apparently would not have survived many days. It was killed with ether, and in the abdominal cavity was found the left testis, measuring 5 cm. long and 2 cm. in diameter, obviously the seat of a large cancer growth. The testis was irregular in shape, nodular, and had on its surface a small cancer nodule about 4 mm. in

diameter, which seemed to be loosely attached to the body of the testis
(fig. 1). Obviously this nodule was an isolated bit of cancer tissue
which probably had been free at one time in the abdominal cavity, had
attached itself to the tunica vaginalis propria, and had grown inde-
pendently of the bulk of the cancer tissue in the testis proper. Indeed,
it was common to see such isolated cancer nodules all over the entire
peritoneal cavity, the omentum as a rule being most heavily laden with
these cancer deposits, with the parietal peritoneum and diaphragm next
in order. It was felt that this specimen would prove ideal for deter-

Fig. 2.—Enlarged drawing of nodule shown in figure 1 to show the extensive
lymph vessel plexus around the base of the cancer mass, but with no lymph vessels
in the cancer nodule itself. The lymph vessels have a superficial and a deep plexus
with numerous communicating channels; × 9.

mining what relationship the lymph vessels in the tunica of the testis
would have to this little nodule. Accordingly, india ink was injected
into the outer layer of the testis, and although the lymph vessels were
seen to fill all about the small nodule, not even the smallest vessel on
the surface of this little cancer mass was seen to become filled with
the injected material.

In figure 2 a magnification of this area is presented, and it can be
readily seen that large lymph vessels and sinuses, some of which are
in a deeper layer, come to the base of the cancer nodule but do not

send any branches into it. A curious feature of the entire plexus is
the intricate and varied pattern of the vessels which intertwine in an
irregular fashion, leaving clear areas, which in turn are surrounded by
a mass of large lymph trunks. The vessels themselves also show the
typical character of lymph vessels by their frequent branching and sud-
den changes in caliber. The general pattern of these vessels is no
different from that seen on the surface of any testis which has no
attached cancer nodule. Obviously the only way of determining what
happened to the lymph vessels under the nodule was by histologic sec-
tion. Serial sections were cut, and it was seen that the lymph vessels
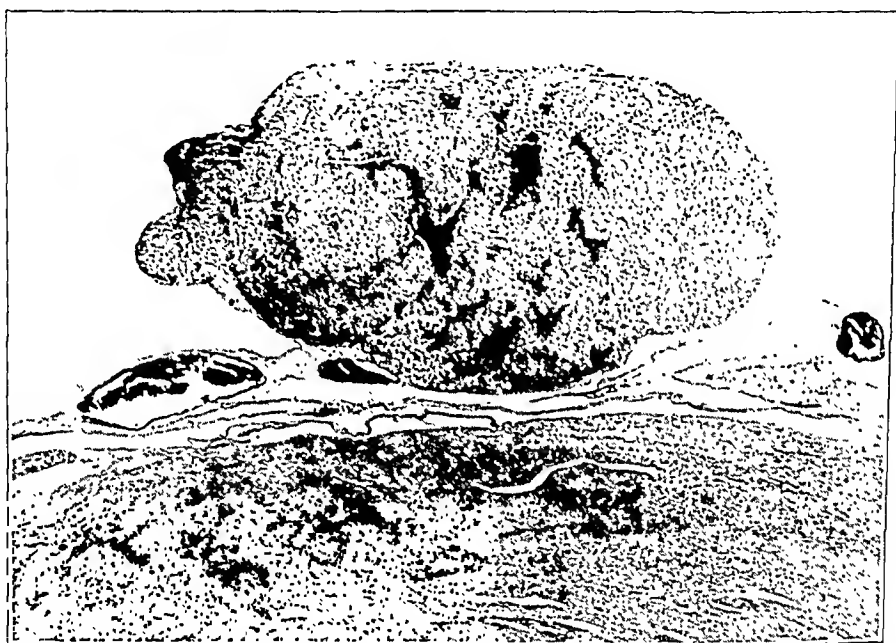
Fig. 3.—Cross-section of the cancer nodule shown in figures 1 and 2. It will
be seen that the nodule is not firmly attached to the body of the testis, and that the
lymph vessels containing the india ink are in contact with the nodule but do not
have any branches that extend into the nodule, indicating that the neoplasm has no
lymph channels of its own. The darker areas in the nodule are areas of cell
degeneration and pyknosis; × 18.

passed underneath the nodule, even at that point at which the nodule
was nearest the main body of the tumor (fig. 3).

Examination of this photograph shows the nodule entirely devoid
of lymph vessels except at its attachment, where the vessels are not only
few in number but are also compressed. No lymph trunks enter the
testis underneath the nodule. In none of the serial sections was there
the slightest evidence of lymph vessels entering the cancer nodule. The
dark-staining areas in the cancer nodule and in the testis represent foci
of necrosis with condensation of dark-staining nuclei, and should not

be confused with the lymph vessels which photograph still blacker because they contain india ink. The scant blood supply to this mass was derived from a few small vessels which passed through the delicate areolar tissue connecting the nodule to the testis. The small tumor mass was quite compact, in spite of the numerous areas of necrosis; no loose areolar tissue surrounded the blood vessels. It is, of course, impossible to predict whether this nodule would have eventually joined the main carcinomatous mass of the testis, but that an amalgamation would have been established seems reasonable from a consideration of the second specimen.

The second specimen was obtained from a rabbit that had been inoculated with cancer thirteen days previously. The animal contracted an acute respiratory infection and died suddenly; the body was still warm when the abdomen was opened. Both testes showed large cancer growths, and the left one also had a small white nodule on its free surface similar to the one just described. In this second case, however, the nodule was flat, and seemed more firmly attached to the testis than in the first case; it was also smaller. Injections of india ink were also made into the lymph vessels in the tunica vaginalis, and it was found that a large and elaborate lymphatic plexus was filled around the base of the nodule, but that no vessels were seen on the surface of the small tumor mass. In all essential points the lymph vessel pattern was the same about the base of the two specimens. Serial sections showed that although a broad base joined the tumor nodule to the testis, nevertheless the area through which cancer tissue was continuous from testis to nodule was relatively small. In fact, the fibrous tissue of the tunica almost formed a completely separating membrane between the cancer tissue of the nodule and of the testis. Again, as in the first specimen, none of the mass injected was found in any part of the cancer nodule, indicating that there was no continuity of the lymph vessels in the tunica vaginalis of the testis with any structure or spaces in the cancer nodule.

Thus far all the observations indicated that there were no lymph vessels in the rabbit carcinoma proper. Accordingly, it was necessary to determine how the lymph vessels which were in the normal testis disappeared. Examination of the serial sections from the two specimens described showed that the cancer cells invaded the lymph vessels, proliferated inside of the lumen of these vessels, eventually filled the lumen, and finally, by fusing with the extravascular cancer, completely destroyed the walls, and with them the last vestige of the lymph vascular system.

Further evidence confirming the observations just described regarding the absence of lymph vessels in rabbit carcinoma was furnished by

fortunate injection into the superficial lymph plexus of the right testis of a rabbit that had been inoculated twenty-three days previously with cancer. Growth of the cancer, however, was not equal in the two testicles, for when the animal was killed, the right testis measured only 45 mm. long and 7.5 mm. in diameter, whereas the left one was 55 mm. long with a diameter of 15 mm. In brief, the right testis was small, with only a moderate cancer growth in the glandular tissue, whereas the left one was more than four times as large. Injection into the superficial lymph vessels of the left testis did not show any penetration into the testis proper, but when the surface lymphatics of the right testis were filled, it was seen that some of the india ink went deeper into the body of the gland. A cross-section of the gland showed that the cancer

Fig. 4.—Sketch of a cleared thin section of a cancer-bearing rabbit testicle showing the lymph vessels of the normal tissue filled with india ink and the cancer areas devoid of the injection. The collecting lymph vessels empty into the large trunks of the mediastinum testis. The proliferating cancer cells are obliterating the lymph vessel in their growth as is seen in the lower portion of the illustrations. A curious feature is the condensation of lymph vessels around one nodule. The marked area is shown at higher magnification in figure 5; $\times$ 12.

occupied the central portion of it, and that the peripheral zone only had received the india ink, indicating that normal testicular tissue was still present near the tunica vaginalis. A thin longitudinal section of the testis cleared in methylsalicylate showed that the lymphatics in the body of the testis formed an elaborate network of vessels which were plexiform, with only small differences in caliber, without any large collecting trunks in the gland itself, but emptying into the large vessels on the surface (fig. 4). Inspection of this illustration shows several areas

entirely devoid of any injected mass, indicating the presence of cancer, with the adjacent normal tissue having a rich plexus of lymph vessels.

The actual structure of the lymphatics can be appreciated better from a study of figure 5, which is an enlargement of the area marked out in figure 4. It will be seen that the vessels form an extensive and elaborate plexus consisting of small vessels with numerous irregular dilatations or sacculations which never exceed a certain size, and which are frequently found parallel to one another. The vessels outline a central area into which they project their sharply pointed processes for a short distance. This central area was demonstrated by histologic section to be solid cancer tissue. In a like manner the other clear area

Fig. 5.—Enlarged drawing of area marked out in figure 4. The lymph vessels filled with ink partly surround the cancer growth, which is devoid of these vessels and is represented by the clear area. It will be noted how relatively small the vessels are at the periphery of the cancer, indicating their compression and obliteration by the neoplasm. The numerous enlargements and constrictions of the vessels are typical of a lymphatic pattern; × 30.

immediately above it in figure 4 was also cancer. But the intervening tissue containing a large number of lymph vessels was predominantly normal testis.

Figure 6, taken from the upper central portion of figure 5, shows a section of several seminiferous tubules partly surrounded by cancer cells and having numerous large lymph vessels partly filled with the injected india ink occupying most of the space between them. In the upper portion of the illustration the cancer tissue is relatively less, the tubules

are more distinct and the lymph vessels are correspondingly large. In the lower part of the figure, however, the tubules are not only compressed but even invaded by the cancer. The lymphatics in their turn are also closed down to a small lumen because of the tumor growth, and it is obvious that the lymph vessels here would have been completely destroyed within a short time. When examined under higher magnification the endothelial cells of the lymphatics can be readily identified.

Some of the steps in this process of invasion deserve a more detailed description because the usual sources of such information are from clinical material in which injections into the lymph vessels have not been made and therefore a confusion might arise as to whether the cancer cells were invading a lymph vessel or a vein. Besides, even such good clinical material as is pictured in Handley's [14] book on the breast does not present such a connected story as can be gleaned from a study of tissue which is, first of all, being invaded by cancer, and, in the second place, has had injections made into its lymph vessels so that they can be easily identified.

It seems that the proliferating cancer cells do not invade a lymph vessel directly, but first attempt to grow around it, and then compress it. During this strangulation process the wall of the lymph vessel is destroyed at one or more points, and the cancer cells thus gain access to the lumen. Once inside the vessel, the malignant growth proliferates along the lines of least resistance. If there is still some lumen left at the point of penetration, the cancer cells will extend out as one mass to fill up the lumen, before they will progress along the inside of the wall to any extent.

Growth of the cancer cells within the lumen extends simultaneously in two directions. Should the lumen at the point of entry be large, the cancer cells will proliferate locally, forming whorls of greater or less size but leaving the vessel wall relatively untouched. India ink was frequently seen within the layers of such whorls, indicating not only the spiral arrangement of the neoplasm, but also its loosely knit character. Should the lymph vessel be invaded at several places about the same time, then the spread of the cancer will be toward the center of the vessel without the production of whorls, unless the vessel has an unusually large diameter. In such an instance the india ink was found as a thin streak in the middle of the vessel.

The other direction in which cancer spreads is directly down the center of the lymph vessel. The proliferating mass resembles much a finger as it is inserted into a glove, except that the cancer mass does not have a tendency to touch the vessel wall, but grows forward for a

14. Handley, W. S.: Cancer of the Breast and Its Operative Treatment, ed. 2, London, A. Murray, 1922.

comparatively long distance. The advancing growth has a relatively blunt tip with its cells having slightly more cytoplasm than ordinarily, and with nuclei situated more in the periphery of the cell body. This central, onward growth is arrested when it meets an object, such as another cancer mass which has appeared independently along the course of the lymph vessel under consideration. At other times the tip becomes attached to the sides of the lymph vessel near a division of the vessel or near a valve. It is remarkable how a thin and delicate valve leaflet can temporarily impede the progress of the growth and guide it toward the
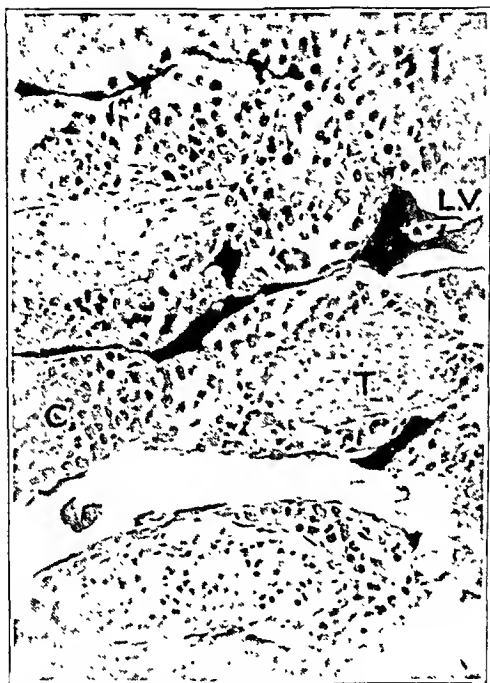
Fig. 6.—Photograph of a histologic section taken vertically at the top center of figure 4 to show how the cancer growth, *C*, is compressing not only the lymph vessels, *L.V.*, filled with india ink, but also the seminiferous tubules, *T*. Note the invasion by the cancer of the lymph vessel at the point, *L.V.*, and the delicate endothelial lining of the lymph vessels; × 130.

center of the stream. Figure 7 shows a relatively large lymphatic containing india ink, with a cancer mass which has impinged on the leaflet, *V*, and has grown along the leaflet without penetrating it. This instance shows well how the cancer growth follows the lines of least resistance.

The preparations which have been described in the preceding paragraphs also serve to convey an idea of the normal distribution of the lymph vessels of the testis. It is true that the lymph vessels of the testis have been described in detail before, the best account probably

being that of Gerster,[15] whose work was substantiated by Regaud.[16] Gerster, however, found it difficult to make injections into the lymph vessels in the testis of rabbits and stated that he could fill only those in the albuginea; he was unable to visualize the lymph vessels in the body of the testis except from histologic preparations stained with osmic acid. All his specimens for injection were obtained from rams and from man. His illustrations show a close resemblance in general pattern to those just described for the rabbit.

The illustrations in figures 1 to 3 thus also serve to give an idea of the normal lymphatic distribution on the surface of the rabbit testis. It

Fig. 7.—Photograph of a histologic section through the tunica vaginalis of a rabbit's testis, showing a lymph vessel, *L*, into which india ink was injected, being invaded by a cancer mass near *C*. It will be noted how the cancer has spread along the valve leaflet, *V*, without penetrating it; × 80.

is true that the testis in every instance was the seat of cancer and therefore not a normal organ; but since the lymph vessels on its surface were not infiltrated by the cancer mass which occupied the body of the testis, it is reasonable to assume that these vessels represented in a measure at least the normal pattern. It must, however, be pointed out that the concentration of lymph vessels about a cancer nodule as is

15. Gerster, R.: Ueber die Lymphgefässe des Hodens, Ztschr. f. Anat. u. Entwcklgsgesch. **2**:36, 1876.

16. Regaud, C.: Les vaisseaux lymphatiques du testicle, Compt. rend. Soc. de biol. **4**:659, 1897.

shown in figure 2, where unusually large vessels have united to form bays about the base of a tumor nodule situated on the surface of the testis, or the similar condensation of lymph vessels about a small cancer mass situated within the body of the gland as is represented by the small circular area in figure 4, cannot be considered normal. But when such areas are disregarded, and only those areas are considered which are free of cancer, then it is reasonable to believe that the lymph vessels in these last named places represented the normal pattern.

Examination of figure 4 shows numerous large lymph trunks situated on the posterior aspect of the testis which receive many tributaries that extend into the body of the testis. A higher magnification of the terminal portion of such a plexus, as shown in figure 5, shows a vessel pattern similar to that described in other parenchymatous organs such as the liver (Lee) and thyroid (Rienhoff).

In brief, from the material obtained in the study of the lymph vessels of the cancer-bearing testes of rabbits, some idea of the distribution and arrangement of these vessels in the normal testes of the animals is obtained. It seems that the lymph vessel pattern for the rabbit's testis is similar to that of the testes of other animals. Apparently injections had not previously been made into the parenchymatous lymph vessels of the rabbit's testis.

COMMENT

Probably the earliest account of lymph vessels in human tumors was given by Krause,[17] in 1863, in a short article which seems to have been overlooked by many who have written on the subject since that time. Krause made injections into tumors which were received still warm from the operating room. His method was to choose cancers that had attached themselves to the skin, and then to make injections into the lymph vessels of the skin with syringe and needle. By this method he claimed to have filled lymph vessels in a myxoma (myxosarcoma?) of the vulva, a scirrhous carcinoma of the breast, two cases of medullary carcinoma of the breast, and a recurrent medullary carcinoma of the hip. His illustrations, taken from the first and last cases, show vessels which certainly resemble lymph vessels. It must be pointed out, however, that no convincing evidence is presented that the lymph vessels were really surrounded by cancer cells. There are no illustrations to show this all-important relationship. Besides, it is quite possible that the vessels into which injections were made were in normal tissue which was about to be invaded by the cancer growth.

An important contribution to the question of whether lymph vessels are present within malignant growths was furnished by Evans in 1908.

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17. Krause, W.: Ueber Lymphgefässe in Geschwülsten, Deutsche Klin. **15:** 377, 1863.

He injected india ink into the distended lacteals on the surface of the small intestine from a patient who had died of round cell sarcoma of the neck with metastases, among other regions, to the bowel. The mass injected penetrated the muscular, submucous and mucous coats. Cleared specimens showed an extensive lymphatic plexus within a small tumor mass situated wholly in the mucosa. Microscopic sections of the tumor nodule demonstrated the mass injected to be within endothelial-lined spaces.

This report of Evans is probably the best that can be found in the literature on this subject at the present time. It is remarkable to find that the sarcoma cells did not compress the lymph vessels, but actually promoted their growth. It would have been interesting to have had more sections through the sarcoma nodule in order to see what blood supply was being furnished, because it is reasonable to suppose that wherever blood vessels find their way in soft tissues, they will always be surrounded by some areolar tissue, and it is therefore possible to have lymph vessels accompanying the blood vessels into a tumor. It is furthermore remarkable to note that in his figure 1 several of the small lymph radicles in the tumor actually extend to the outermost portion of the tumor; ordinarily lymph vessels never are found so near to the lumen of the bowel.

It must also be pointed out that Evans has not given a convincing account of the tumor with reference to its lymph vessels in so far as he has made out a clear case for the proposition that the tumor has replaced normal tissue and that the injected lymph vessels are newly formed in the tumor and were not originally situated in the tissue, being only distorted and dislocated by the neoplasm (MacCallum [18]). Furthermore, in his figure 2, the so-called proliferating endothelial cell may possibly be viewed as one that is being compressed by the tumor growth rather than a cell that is working its way into a mass of sarcoma cells.

Besides, there is also the possibility that an inflammatory process might have been part of the mass, particularly in view of the limited description of the cytology of this tumor and its close proximity to the lumen of the bowel. On this basis, following the work of Coffin,[19] it is reasonable to consider some of the lymphatics as being in granulation tissue.

It is possible, however, that a great difference exists between the relationship of lymph vessels in human sarcoma and in the carcinoma of the rabbit. Perhaps the nature of the growth alone is responsible for this variation. The chief points that indicate that there are no lymph vessels within rabbit carcinoma are these: In the first place, the

18. MacCallum, W. G.: Personal communication.

19. Coffin, T. H.: On the Growth of Lymphatics in Granulation Tissue, Bull. Johns Hopkins Hosp. **17**:227, 1906.

specimen described in figures 1 to 3 demonstrates that if lymph vessels were present in the nodule, the only means of pouring their contents into other lymphatics and thus establishing drainage must necessarily have been through the lymphatics on the surface of the testis where the cancer nodule was attached. And even though lymph vessels were demonstrated at the base of the nodule, there were no extensions of these vessels, or communications with these vessels, within the small tumor mass itself. It might be argued that the isolated bit of cancer tissue which later formed the nodule also contained lymphatic endothelium, and that as the nodule grew the lymphatic system increased likewise. But even if this were true, no avenue for the escape of the lymph would have been demonstrated. It seems unlikely that any single vessel, much less any group of vessels, could have avoided the rich plexus of lymph vessels which were outlined in the tunica vaginalis. Furthermore, the cancer nodule was compact, with no spaces which might be taken for lymph vessels, and with the characteristic poor blood supply which was derived from the testis, and along the vessels of which no possible spaces for lymph vessels were seen.

In the second place, the rabbit cancer cells penetrated the lymph vessels and entirely supplanted them. Not only were lymph vessels destroyed, but all normal tissue disappeared, and in its place there developed a mass of cancer cells which extended beyond the ordinary confines of the normal tissue. Now, the only possible way for the cancer growth to get a lymph system would be to have these vessels follow in the wake of the cancer growth, and at all events such lymph vessels must communicate with those on the surface in order to have any drainage at all. But no such lymph vessels were seen in the tumor when injection was made into superficial vessels. There is still a possibility that the proliferating cancer cells in their growth might spare a few vessels and thus leave a skeleton lymph system for the tumor; however, examination of the sections showed conclusively that the cancer cells destroyed all tissue that was in the way of its growth. The only time that lymph vessels were seen about cancer cells was when there was normal tissue at hand, and the lymph vessels were found in this normal tissue.

The most pertinent article on the subject under discussion is by Goldmann, written in 1911. Being interested in the biology of neoplasms, particularly from the point of view of their blood and lymph supply, he made numerous vascular injections of mouse carcinoma transplanted into the peritoneum of animals of this same species. He was able to show conclusively that a tumor mass which had attached itself to the serous surface of the intestine received an extensive blood supply from the bowel, but in no instance were any lymph vessels seen to extend from the bowel wall to the tumor mass. Ink was injected into

the lymph vessels of the bowel with a fine needle and a syringe. Injection was made only into the submucosa because this layer is apparently the only one in the intestinal wall of the mouse that has a lymph plexus. These observations of Goldmann are in absolute agreement with those reported herewith on rabbit carcinoma. One interesting point of difference, however, must be mentioned. In the mouse, the lymphatic plexus nearest the cancer was separated by two layers, the muscular and serous coats, whereas in the rabbit the cancer mass was situated directly on the serous coat into the lymph vessels of which injection was made. Apparently even the greater proximity of lymph vessels and cancer did not facilitate any lymphatic extension into the carcinoma.

SUMMARY AND CONCLUSION

India ink was injected into cancer-bearing testes from ten rabbits in order to determine the relationship between the lymph vessels of the testis and of the cancer mass. In no instance were lymphatics found in the cancer mass. Incidentally, the lymph supply of the normal testis of the rabbit was observed and briefly described. Examination of the literature makes it doubtful whether any true newly formed lymph vessels were ever observed in cancer tissue. In conclusion, it may be stated that transplantable rabbit carcinoma does not have any lymph vessels.

RECONSTRUCTION OF A CONJUNCTIVAL SAC WITH THIERSCH GRAFTS

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The epithelial inlay graft described by Esser [1] and developed extensively by Gillies [2] has many useful applications in plastic surgery. We applied the method successfully in reconstructing a conjunctival sac which was completely destroyed by a chemical burn.

REPORT OF A CASE

The patient who presented this unusual plastic problem was a man of 37, a plumber, whose previous history was not significant. He was injured on March 13, 1929, when some alkaline drain compound was thrown in his face, and he was admitted to St. Luke's Hospital on that date. Physical examination showed nothing of importance except for superficial second degree burns scattered over the face, neck and upper part of the chest, hyperemia and edema of the tongue and mucous membranes of the mouth, marked chemosis of the right eye, some haziness of the cornea and marked edema of the lids. There was moderate injection of the conjunctivae of the left eye.

The hyperemia of the mouth cleared up in three or four days with frequent irrigations with salt solution, and the superficial skin burns treated with 5 per cent tannic acid jelly were clearing up rapidly when the patient was discharged from the hospital on March 19, six days after his injury. The burn of the right eye, however, was a serious one with involvement of the ciliary body to such an extent that the corneal circulation was impaired, with resulting necrosis of the latter and destruction of the anterior chamber. Enucleation of the eye was advised, but for several weeks the patient refused to have this done. He finally consented and was admitted to the ophthalmologic service on April 18. Enucleation was done under gas-oxygen anesthesia on the following day (Dr. Jacoby), and a glass globe was implanted in the orbit. The conjunctivae were found to be almost completely destroyed, and the eyeball was dissected from a mass of freely bleeding granulations. The patient was again discharged from the hospital on April 25, six days after the enucleation. In spite of the low grade infection present, the sutures in the bulbar fascia held and the glass globe was fortunately retained. Since the conjunctival sac was completely destroyed, the eyelids soon became adherent tightly to the bulbar fascia over the glass globe and to each other.

At this juncture, the condition of the injured orbit was roughly that depicted in figure 1. (Unfortunately no photograph was taken at this time.) The lids were tightly sealed together and depressed in an unsightly manner. It was decided to attempt to reconstruct the conjunctival sac by a modification of the Esser inlay method to enable the patient to wear an artificial eye.

The patient was readmitted to the hospital on June 7 for this operation, which was done the following day under nerve block with procaine hydrochloride (Dr. Glover). First the margins of the lids were dissected free and the underlying scar tissue was removed, undermining the lids nearly to the orbital margin. A mold of sterilized dental composition, softened in hot water, was then fashioned to fit snugly in the pocket formed under the lids (fig. 2). The cavity was then packed with gauze wet with hot salt solution to control the bleeding, while a thin Thiersch graft was cut from the inner aspect of the arm where the skin is thinnest and of finest texture. (We prefer a long, narrow-bladed amputation knife for cutting these grafts. It is absolutely essential that the surface to be grafted be absolutely free from bleeding when the graft is applied.) The graft was then wrapped carefully about the mold, with the cut or deep surface of the graft outside. This mold

Fig. 1.—Appearance of the patient after enucleation. The right conjunctival sac had been completely destroyed by a chemical burn.

covered with the Thiersch graft was then inserted into the pocket prepared for it, and fine dermal, mattress sutures were passed through both margins of the lids, catching the edge of the graft to keep it from slipping (fig. 3). When the sutures were tied, the margins of the lids were approximated. A pressure dressing of gauze and bandage wet with physiologic solution of sodium chloride was applied over the eyelids, it being important that no dead space develop between the graft and its bed during the first twenty-four hours. Oiled silk was bandaged over the moist dressings to minimize evaporation. Warm physiologic solution of sodium chloride was added every four hours. The patient left the hospital on the sixth postoperative day. On the eighth day the sutures were removed, and on the tenth day the mold was allowed to come out and the cavity was flushed to clear it of epithelial débris. It was then apparent that the graft had taken in its entirety with the exception of two small spots, 2 or 3 mm. in diameter. Since these small granulating spots did not epithelize rapidly, on June 21 they were curetted, small grafts applied to them, and the cavity packed tightly with moist gauze. These grafts vascularized readily, completing the epithelization of the pocket. The patient continued to wear the mold in the newly formed cavity, in the attempt to keep it from contracting. But, as is well known, Thiersch grafts have the unfortunate habit of contracting for some weeks following their application, and here the contraction
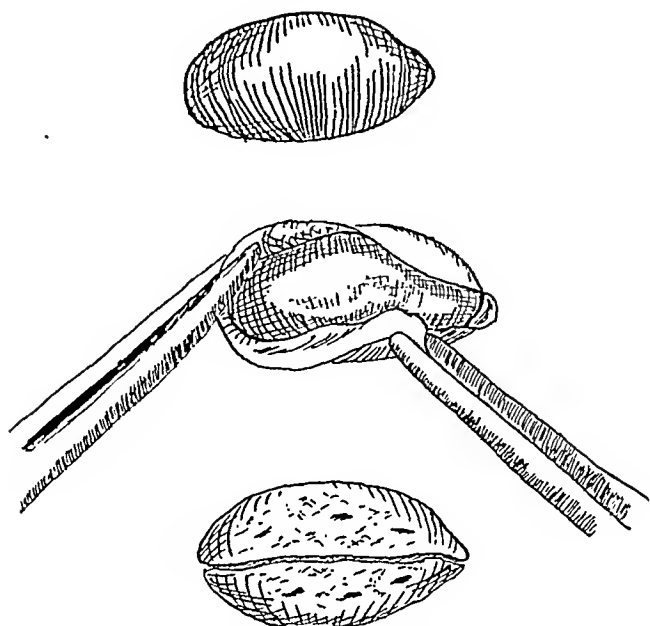
Fig. 2.—The nutmeg-shaped mold of dental composition is made to fit the pocket dissected beneath the eyelids, as shown at the top. The middle and lower sketches show the manner in which the Thiersch graft is wrapped about the mold. The graft has been perforated to prevent accumulation of serum beneath it.
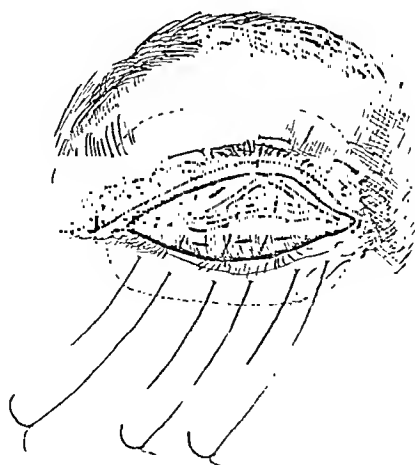
Fig. 3.—The mold with thin graft wrapped about it is now in the pocket and sutures are placed through the margins of the lids, catching the edges of the graft. The dotted lines indicate the extent to which the eyelids are undermined.

of the grafts and spasm of the orbicularis oculi soon forced the mold out, and a small artificial eye (or shell) was substituted. After two or three weeks more this also was forced out by the contraction of the cavity.

We were then faced with the necessity of greatly enlarging the skin-grafted pocket which had become too small to retain any solid object within it. Accordingly, another inlay graft was done under local anesthesia, on August 30, five and one-half months after injury. At this time we did an external canthotomy to serve the double purpose of giving more room and to stop the contraction of the orbicularis oculi temporarily, since we felt the latter factor had caused part of our previous difficulty. Incisions were then made in the skin-lined pocket parallel to the margins of the lids, and the lids were widely undermined again (fig. 4 A). A
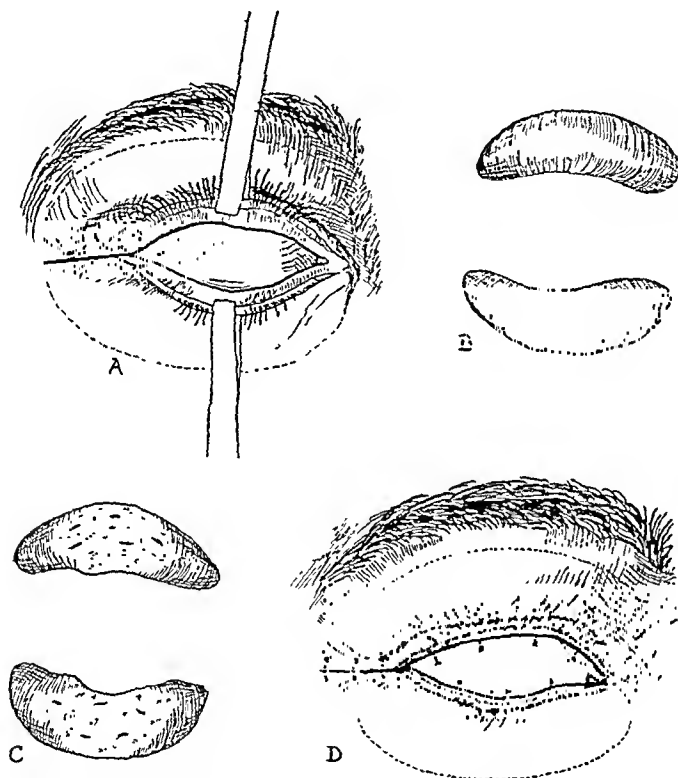
Fig. 4.—The second Esser inlay graft. A, heavy lines mark the incisions for the external canthotomy and undermining the lids, and the dotted lines show the extent to which the eyelids were undermined. B, a mold or stent is made to fit under each eyelid. C, Thiersch grafts are wrapped about each mold. D, the molds covered with thin grafts are sutured in place.

dental composition mold was then made to fit the pocket under each lid (fig. 4 B). Thiersch grafts were cut and wrapped about these molds or "stents"[3] (fig. 4 C) which were introduced into the pockets in the upper and lower lids, and the skin approximated over them with fine dermal sutures (fig. 4 D). Moist salt solution compresses were then applied as before, and the patient was allowed to go home. At the end of seven days the sutures were removed and the molds were allowed to

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3. These molds are called "stents" by Gillies, after Stent who introduced dental composition.

Fig. 5.—The large skin-lined pocket resulting from the Esser inlay grafts.

Fig. 6.—Appearance of the patient with artificial eye in place three years after injury.

Fig. 7.—Appearance of the skin-lined conjunctival sac three years after injury.

come out, forming a larger skin-lined pocket, with room to spare (fig. 5). A large mold that would completely fill the cavity was made and kept in place for two months, until it was felt that all the contraction reasonably to be expected had taken place. At the end of this time the cavity was a little too large to hold an artificial eye well, and a canthoplasty was done (Dr. Jacoby) to narrow it.

The patient wore a large shell for several months, but for two years or more he has worn the eye that is shown in the photograph taken on March 30, 1932 (fig. 6). The skin-lined conjunctival sac was in excellent condition at this time, three years after injury, and no further contraction or ulceration had taken place. It was gratifying to see how well the skin had adapted itself to its new location, because we were rather apprehensive lest it should contract more or ulcerate from the constant pressure of the artificial eye. It does not seem likely that this will occur later, since the grafted skin has had adequate time to become stabilized (fig. 7).

In retrospect, we believe a large disk-shaped mold could have been used with greater satisfaction at the time of the first inlay graft in place of the nutmeg-shaped mold we used, and perhaps a second stage operation would have been avoided.

Miss Jane Van Gordon made the pen and ink sketches.

PERICARDITIS SIMULATING AN ACUTE CONDITION OF THE ABDOMEN

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During the past few years, three patients have been admitted to the surgical service at Cook County Hospital with a diagnosis of acute appendicitis. All three underwent appendectomies, and in each instance the appendix was grossly and microscopically normal. Subsequent to laparotomy, a definite pericardial friction rub developed, and a diagnosis of rheumatic pericarditis was made.

The incidence of acute abdominal pain at the onset of rheumatic fever, particularly with acute pericardial involvement, is seen not uncommonly. The mechanism of its production is obscure, and its clinical recognition difficult. Geissinger [1] recorded a case in a boy 5 years of age who had a sudden onset of abdominal pain with fever and vomiting accompanied by marked rigidity of the abdominal muscles. A laparotomy was done, and a normal appendix was found. On the fourth day postoperatively polyarthritis developed, and on the tenth day a typical pericardial friction rub was heard. This author commented on the absence of similar 'case reports in the literature. Hyman,[2] commenting on Geissinger's report, added a second case in a child 6 years of age with a similar acute onset of abdominal pain, tenderness, rigidity and fever. Although the conditions of the abdomen seemed to require surgical intervention, operation was delayed because of cardiac findings. The following day acute arthritis of the ankle appeared, and in the next twenty-four hours fully developed rheumatic fever with large pericardial effusion was present.

Fussel and McKay [3] reported three cases of pericarditis with pain referred to the right iliac fossa. None of these patients was subjected

1. Geissinger, J. D.: Acute Abdominal Pain in Rheumatic Fever, J. A. M. A. 94:1427 (May 3) 1930.

2. Hyman, A. S.: Abdominal Pain at the Onset of Rheumatic Fever, J. A. M. A. 94:1782 (May 31) 1930.

3. Fussel, M. H., and McKay, J. A.: Symptoms of Appendicitis in Acute Pericarditis, Am. J. M. Sc. 163:40 (Jan.) 1922.

to operation, since pericardial findings were manifest on entrance. In one, autopsy revealed plastic pericarditis and a normal appendix.

Wynter [4] reported two cases, one of which was diagnosed perforated gastric ulcer and the second acute appendicitis. Neither revealed pathologic involvement at laparotomy, and in both signs of pericarditis subsequently developed. This author believed the absence of abdominal respiratory movements of value as a diagnostic sign in pericarditis.

Holden [5] cited three cases of a similar nature, in which acute abdominal conditions were diagnosed, in which laparotomy was performed. Pericardial rub developed in each from twenty-four to forty-eight hours postoperatively. He stated that while the relationship of right-sided pneumonia to an acute condition in the abdomen has been stressed, textbooks are silent on the incidence of abdominal symptoms in pericarditis.

In analyzing the mechanism of the production of abdominal symptoms in rheumatic pericarditis, a number of factors must be considered: (1) referred pain from the thorax, (2) rheumatic myositis of the abdominal muscles, (3) rheumatic peritonitis, (4) involvement of the mesenteric glands and (5) true rheumatic appendicitis.

REFERRED PAIN FROM PATHOLOGIC INVOLVEMENT OF THE THORAX

There is considerable divergence of opinion expressed in textbooks regarding the incidence of pain in pericarditis. Holt [6] stated that localized pain and tenderness are usually present in acute rheumatic pericarditis. Norris and Landis [7] stated that pain may be entirely absent or may be of a sharp stabbing character, usually felt over the heart but at times radiating into the abdomen or to the left shoulder or left side of the neck. Allbutt [8] stated that the patient usually complains of a dull ache rather than of acute pain. In other instances, the pain varies from slight discomfort to severe pain aggravated by movement, deep inspiration or cough, localized at times to the epigastrium or radiating to the neck and shoulder blade or shoulder. McKenzie [9] described dry pericarditis as an essentially painless disease,

4. Wynter, W. E.: Absence of Abdominal Respiratory Movements as an Indication of Pericarditis, Clin. J. **42**:185, 1913.

5. Holden, W. B.: Pericarditis, Report of Three Cases in Which Early Symptoms Were Entirely Referred to the Abdominal Cavity, Northwest Med. **19**:230 (Sept.) 1920.

6. Holt and Howland: Diseases of Infancy and Childhood, New York, D. Appleton and Company, 1926.

7. Norris and Landis: Diseases of the Chest, Philadelphia, W. B. Saunders Company, 1918.

8. Allbutt, C., in the Oxford System of Medicine, New York, Oxford University Press, 1920, vol. 2, p. 261.

9. McKenzie, James: Diseases of the Heart, New York, Oxford University Press, 1925.

asserting that there is no distinctive sign characteristic of it other than the presence of a friction rub. When pain is present, accompanying myocardial disease will invariably be found. He said that some writers describe pain as a symptom of pericarditis and that it is possible that a dull ache may be present. When severe pain is aggravated by respiration, it is due to a coincident pleurisy.

From an experimental point of view, there is little literature on pericardial pain. Capps,[10] commenting on the variability of the picture of pain in pericardial pathologic involvement, carried out an investigation to determine what structures within and adjacent to the pericardium were capable of producing pain. This was determined by direct irritation of the pericardium in patients with a large amount of pericardial effusion, a silver wire being inserted through a trocar. Four cases were investigated in this manner. In three instances, no pain was noted on puncture of the pericardium at the level of the fourth interspace. In two punctures at the level of the fifth interspace and in one puncture at the level of the sixth, pain was felt in the neck. Irritation of the serous surface of the visceral pericardium by the wire demonstrated this area to be insensitive to pain, and the serous surface of the parietal pericardium also yielded negative results as far as it could be explored. From his investigations, Capps concluded that dry pericarditis is a painless disease, as McKenzie had stated. Further, the presence of pain in pericarditis indicates involvement of structures outside the pericardium, especially the pleura.

Alexander and his associates [11] presented observations on the sensitivity of the visceral and parietal pericardium in a patient whose heart had been exposed as a result of a pericardiotomy for purulent pericarditis. These authors found that pressure on the inner surface of the parietal pericardium produced pain referred to the chest and abdomen. No other stimulus to the heart, pericardium or diaphragm caused reference of pain to any part of the body.

Unverricht,[12] using the thoracoscope, was able to make observations under physiologic conditions. He found the visceral pleura insensitive to touch, heavy pressure and superficial needle prick. In the case of the parietal pleura, light touch was usually not felt. Pressure and needle prick were felt but not definitely localized. Heat was felt as pain. The diaphragmatic pleura in its central portion gave pain in the neck and shoulder of the same side when stimulated by pressure or

10. Capps, J. A.: Pericardial Pain, Arch. Int. Med. **40**:715 (Nov.) 1927.

11. Alexander, J.; MacLeod, A. G., and Barker, P. S.: Sensibility of the Exposed Human Heart and Pericardium, Arch. Surg. **19**:1470 (Dec.) 1929.

12. Unverricht: Sensibilitätsprüfungen von Pleura und Perikard, Klin. Wchnschr. **6**:855, 1927.

needle prick. In the peripheral portion painful stimuli were noted as an unpleasant sensation in the thorax and upper part of the abdomen of the same side, not definitely localized.

Simenauer,[13] continuing the observations of Unverricht in a larger series of cases, obtained essentially the same results. He was able to test the response to stimulation of certain areas of the pericardium in three cases. Pressure on the parietal pericardium in the region of the apex gave a sense of pressure referred to the left arm especially along its medial aspect, suggestive of the reference of pain in angina pectoris. In a second case, the pericardium of the left ventricle was stimulated, yielding no response to touch and to light pressure. Heavy pressure produced an unpleasant sensation at the level of the sixth rib just inside the midclavicular line. Sticking with a pointed instrument was not felt. In the third case, the pericardium was thickened, and this patient felt no stimuli. The author was unable to draw any definite conclusions regarding pericardial pain from these observations.

In an analysis of the mechanism of abdominal pain in pericarditis, a study of the innervation of the adjacent organs is essential. The researches of Capps,[10] Unverricht[12] and Simenauer,[13] and the clinical observations of such men as McKenzie[9] indicate that the pain in acute rheumatic pericarditis is dependent to a considerable degree on involvement of contiguous structures. The innervation of the diaphragm is derived from two sources, the phrenic nerves and the lower six intercostal nerves. The phrenic nerves are derived principally from the fourth cervical nerves, though they receive fibers from the third and fifth nerves as well. The afferent fibers originate from the cells in the dorsal root ganglions of the third, fourth and fifth spinal nerves. In the lower part of the chest, the phrenic nerves lie between the pericardial pleura and the parietal pericardium, and give off branches that constitute the chief nerve supply of these structures. On reaching the diaphragm, terminal branches spread out over this structure beneath the diaphragmatic pleura. These fibers are distributed to within a few centimeters of the costal margins ventrally and laterally. Branches of the right nerve penetrate the diaphragm and give off rami to the deep muscular structures, the falciform ligament and the peritoneal covering of the upper surface of the liver. The left nerve similarly sends penetrating branches which supply the deep muscular layers of the left dome of the diaphragm and spread out over the central portion of the diaphragmatic peritoneum.

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13. Simenauer, Erich: Die Sensibilität von Pleuren, Perikard, und Peritoneal-überzug des Diaphragma mit besonderer Berücksichtigung des Nervus phrenicus, Ztschr. f. Tuberk. **48**:273, 1927.

Experimental data, such as the work of Capps[11] and Capps and Coleman,[15] indicate that the sensory innervation of the anterior two thirds of the diaphragmatic pleura and peritoneum is derived from the phrenic nerves to within a short distance of its ventral and lateral margins. Stimulation of this central diaphragmatic surface gives rise to the familiar shoulder pain. The explanation for this phenomenon lies in the fact that the cutaneous innervation of this area is derived from the branches of the third and fourth cervical nerves. When the sensory fibers of the phrenic nerve are stimulated, pain is referred by the brain to the cutaneous distribution of the third and fourth cervical nerves and not to the position of the diaphragm at all. The explanation for the wide separation of the area of stimulation and the region of reference of pain lies in the developmental history of the diaphragm. This structure is originally formed in the neck and begins to migrate caudally at an early period of intra-uterine life, concomitant with the development of the lung buds. With the full development of the lungs, the diaphragm reaches its permanent position at the lower end of the thorax.[16] In view of this innervation, one would expect shoulder pain to be a common manifestation of pericarditis, as Capps[10] has pointed out.

The nerve supply of the lateral rim of the diaphragm and of the posterior one-third not supplied by the phrenic nerve is derived from the intercostal nerves. Irritation of the posterior one-third and of the lateral and ventral border zones of either surface of the diaphragm causes referred pain over the cutaneous area supplied by the lower six thoracic nerves. This results in referred pain over the upper part of the abdomen and to a lesser extent over the lower quadrants.[17] The developmental explanation for this second innervation lies in the origin of the posterior one-third and the peripheral border of the diaphragm from the adjacent body wall.

In view of the clinical and experimental data at hand, therefore, we may state that the picture of pain in pericarditis is dependent to a considerable extent on involvement of adjacent structures. When the fibrous pericardium and pleura in the region of the diaphragm are involved, pain will occur in the region of the shoulder or neck from irritation of the afferent fibers of the phrenic nerve and reference to

14. Capps, J. A.: An Experimental Study of the Pain Sense in the Pleural Membranes, Arch. Int. Med. **8**:717 (Dec.) 1911.

15. Capps, J. A., and Coleman, G. H.; Experimental Observations on the Localization of Pain Sense in the Parietal and Diaphragmatic Peritoneum, Arch. Int. Med. **30**:778 (Dec.) 1922.

16. Morley, John: Abdominal Pain, Edinburgh, E. & S. Livingstone, 1931.

17. Meyers, J. A.: The Normal Chest, Baltimore, Williams & Wilkins Company, 1927.

the cutaneous area supplied by the third and fourth spinal nerves. When the posterior mediastinum is involved, pain will be referred through the lower intercostal nerves to the abdomen.

Abdominal pain occurs also in the absence of definite evidences of carditis. Coburn,[18] in a study of one hundred and sixty-two patients with rheumatic phenomena, encountered severe abdominal pain in the right lower quadrant more than forty times. In five of these a normal appendix was removed, and shortly afterward unquestionable rheumatic manifestations made their appearance. Recrudescences of rheumatic manifestations later developed in some of these patients, with return of the abdominal pain in the right lower quadrant. Baudet[19] reported a case in which the onset of rheumatic fever occurred with abdominal pain. An appendectomy was done, revealing a normal appendix, and twenty-four hours later typical rheumatic polyarthritis was present. Costedoat[20] cited a similar case in a person with polyarthritis. He suggested the possibility of fixation of the rheumatic virus in the abdominal wall.

Pearson[21] described the abdominal pain of rheumatic fever as an acute sharp pain seated deeply in the epigastrium, recurring in short paroxysms from four to five times daily. The paroxysms were often precipitated by sudden exertion; there was no associated nausea or vomiting, and the incidence bore no relationship to the taking of food. There were no soreness of the abdominal muscles and no tenderness, superficial or deep. Typically, these repeated attacks recurred daily for several days, and then definite rheumatic manifestations appeared. The author attributed this pain to gastric catarrh dependent on the rheumatic infection.

Hutchison[22] described rheumatism or fibrositis of the abdominal muscles as a common manifestation in childhood, and one that may easily simulate acute conditions in the abdomen. He stated that this condition may easily be distinguished by the fact that the pain comes on when the affected muscle is thrown into action, e. g., when the patient tries to sit up in bed without using his hands. There may be considerable tenderness, especially when the muscle is contracted. This

18. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931.

19. Baudet: Acute Articular Rheumatism Simulating Appendicitis, Bull. et mém. Soc. d. chir. de Paris **57:**265 (Feb. 28) 1931.

20. Costedoat, M.: Début à forme péritonéale de la maladie rhumatismale, Bull. et mém. Soc. méd. d. hôp. de Paris **53:**1353 (Dec. 2) 1929.

21. Pearson, S. V.: Abdominal Pain in Acute Rheumatism, Brit. M. J. **1:** 1120, 1904.

22. Hutchison, R.: Diagnostic Significance of Abdominal Pain in Children, Brit. M. J. **1:**1, 1921.

tenderness differs from that due to inflammation of an underlying organ by the fact that it is also present when the abdomen is grasped or compressed laterally. Still [23] similarly described rheumatic myositis as a common cause of abdominal pain in childhood.

Wood and Eliason [24] recently reviewed the problem of rheumatic peritonitis as a cause of abdominal pain in rheumatic conditions. They cited a considerable number of cases reported in the literature of peritoneal involvement presumably on a rheumatic basis. They reported a case of acute abdominal syndrome in a rheumatic patient in whom laparotomy was done and definite peritoneal pathologic changes found. The appendix was normal. Subsequently, massive pericardial effusion developed. Cultures from both the peritoneal and the pericardial fluid were sterile. On the evidence collected, Wood and Eliason believed that true rheumatic peritonitis may occur more frequently than has been thought heretofore, and may account for the abdominal pain in some cases of rheumatic fever.

The presence of acute adenitis of the mesenteric glands, as pointed out by Brennemann [25] in the case of infections of the respiratory tract, must be borne in mind as a possible causative factor in the abdominal pain of rheumatic fever. The possibility of such involvement of lymphatic structures is repeatedly encountered in the literature.

Finally the occurrence of true acute appendicitis in the presence of acute rheumatic fever is an important possibility which must not be overlooked.

REPORT OF CASES

CASE 1.—*History.*—N. M., a white boy, aged 9, was admitted to the children's surgical ward of Cook County Hospital on Nov. 15, 1928, complaining of pain in the abdomen of four days' duration. He had had a sore throat and headache for two days prior to the onset. The pain was first noted in the region of the umbilicus, and after several hours shifted to the right lower quadrant and the right lumbar region. Nausea was present at the onset, and vomiting occurred once after the administration of a cathartic. Loose stools were present for three days prior to admission.

Examination.—Physical examination of the chest gave negative results, except for roughening of the first sound at the apex of the heart. There was generalized tenderness over the entire abdomen, most marked over the entire right side. Slight rigidity was noted over both upper quadrants, most marked on the right. Peristaltic sounds were present. The child appeared acutely ill, with a temperature of 102.4 F. and a leukocytosis of 23,000. Urinalysis was negative. A diagnosis of acute appendicitis was made and a laparotomy done. The appendix was grossly and microscopically normal, and no peritoneal involvement was present.

23. Still, G. F.: Common Disorders and Diseases of Children, ed. 2, London, H. Frowde, 1912.

24. Wood, F., and Eliason, E. L.: Rheumatic Peritonitis, Am. J. M. Sc. **181**: 482 (April) 1931.

25. Brennemann, J.: The Abdominal Pain of Throat Infections, Am. J. Dis. Child. **22**:493 (Nov.) 1921.

Course.—Following operation, the boy had a continuous fever of from 101 to 102 F. On the fifth day postoperatively, he complained of pain in the knees. The joints were swollen, hot and tender, and acute rheumatic fever was diagnosed. On the seventh day, postoperatively, cardiac findings were noted, consisting of enlargement, palpable thrill, systolic and diastolic murmur and a loud friction rub over the entire precordium. At this time the boy gave a history of repeated attacks of severe rheumatism. A diagnosis of rheumatic fever with pancarditis was made, and the child was transferred to the medical service. The course was protracted, with several recurrences of fever, pain in the joints, precordial pain and pain in the neck. On Aug. 17, 1929, the patient was finally discharged with a diagnosis of chronic endocarditis with mitral stenosis and insufficiency and aortic regurgitation.

CASE 2.—*History.*—C. S., a colored boy, aged 12, was admitted to the surgical service on June 13, 1929, complaining of pain in the right side, headache and pain in the right knee of six days' duration. The onset was abrupt, with sharp stabbing pain in the epigastric region. Shortly afterward, the pain shifted to the right lower quadrant, where it remained constantly, though on one occasion it radiated down both thighs. The child had never had a similar attack previously. Nausea was present but no vomiting. Pain in the right knee had been present during the entire week, and was severe enough to confine the patient to bed. He had had about five of these attacks during the past three years, usually lasting about one month. The bowel movements were normal during the entire course.

Examination.—The boy appeared subacutely ill and in considerable pain. The results of examinations of the heart and lungs were entirely negative. There was tenderness in both lower quadrants of the abdomen, especially on the right, with slight rigidity over the right rectus muscle. Peristaltic sounds were audible. On rectal examination, tenderness was noted in the right lower quadrant. The right knee was painful with much muscular spasm.

Course.—A diagnosis of appendicitis was made, and an appendectomy done. The appendix was grossly and microscopically normal. Postoperatively, the boy had a continuous fever, the temperature being as high as 103 F. On the second day, a pericardial friction rub was heard, and a diagnosis of rheumatic pericarditis was made. The course was stormy, with high fever and considerable cardiac embarrassment showing evidence of patchy consolidation in the fields of both lungs at one time. The patient was finally discharged from the hospital on July 23, with a diagnosis of chronic endocarditis with mitral insufficiency.

CASE 3.—*History.*—F. J., a colored boy, aged 13, was admitted to the surgical service on Sept. 4, 1931, complaining of abdominal pain of two days' duration. Three days prior to admission, he had had a headache and pain in the neck. The following morning he noted a diffuse pain in the epigastrium. In a few hours, the pain shifted to the right lower quadrant, where it persisted as a dull ache. There was no associated nausea or vomiting, and the bowel movements were normal.

Examination.—The child did not appear acutely ill or in pain. The temperature on admission was 99.8 F. A systolic murmur was present at the apex and transmitted to the axilla. There was moderate tenderness in the right lower quadrant of the abdomen just to the right of the navel, with no muscular rigidity. There was slight rebound tenderness, and peristaltic sounds were present. The leukocyte count was 22,000, the urine negative.

Course.—A diagnosis of appendicitis was made, and an appendectomy done. Pathologically, the appendix was normal grossly and microscopically. There was no apparent peritoneal involvement at laparotomy. Postoperatively, the child had a constant temperature around 101 F. On the fourth day, he complained of pain

in the left side of the chest, and a definite pericardial friction rub was heard. He was transferred to the medical service with a diagnosis of rheumatic pericarditis. The course was uneventful and he was discharged on October 9, in good condition. On several occasions, he complained of precordial pain and pain in the right side of the neck.

COMMENT

In reviewing these three cases, several factors of diagnostic importance are apparent. Two of the patients gave a definite history of preceding attacks of rheumatic fever. In the third, no rheumatic history was obtained but on physical examination, typical findings of mitral insufficiency were noted. In all three, symptoms suggestive of a generalized systemic infection, such as headache, sore throat and fever, were present before the onset of the abdominal pain. In case 2, definite arthritis of the right knee, which was so severe as to constitute a prominent part of the complaint, was present at the onset.

The character of the abdominal pain in these cases offered the greatest difficulty in differentiating the condition from a surgical condition in the abdomen. In each instance the onset was abrupt, with diffuse pain located in the epigastrium or in the umbilical region and later shifting principally to the right lower quadrant. It was associated with some tenderness in one or both lower quadrants and with slight or no muscular rigidity. Definite localization of tenderness and rigidity was not present in any of these cases. Pain in the neck was complained of in two of the cases, at the onset in one and after the development of signs of pericardial involvement in the other. This pain was prominent enough to be mentioned by the boys without leading questions. Direct questioning as to the incidence of pain in the neck or shoulders and examination for cutaneous hyperalgesia over these areas might be of great diagnostic aid in similar cases.

In the past, the incidence of symptoms simulating an acute condition of the abdomen in pneumonia located in a lower lobe has been stressed. As a consequence, this possibility is kept prominently in mind whenever patients are seen with acute abdominal pain. If the incidence of such a syndrome in rheumatic infections and in acute pericarditis was similarly thought of, undoubtedly the error made in diagnosis would be much less frequent. It may be said, however, that when a reasonable doubt exists as to the presence of acute appendicitis, it is much wiser to err on the side of safety and explore the abdomen.

SUMMARY AND CONCLUSIONS

1. There is considerable variability in the picture of pain in rheumatic pericarditis.

2. Experimental evidence indicates that the presence of pain is dependent on involvement of contiguous structures.

3. The mechanism of its production is discussed.

4. Three cases of rheumatic pericarditis with abdominal symptoms, in which appendectomies were performed, are reported.

5. A rheumatic history, the presence of other rheumatic manifestations, the incidence of pain in the shoulder and the atypical abdominal findings are stressed as of diagnostic value.

6. Pericardial involvement merits equal consideration with pleural involvement, e. g., in pneumonia of the lower lobe of the right lung, in differentiating between acute abdominal conditions, particularly in childhood.

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SARCOMA, MELANOMA AND LEUKOSARCOMA OF THE RECTUM

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DETROIT

The purpose of this article is to place on record 7 cases of malignant neoplasm of the rectum; 2 of spindle cell sarcoma, 1 of myosarcoma, 3 of melanoma and 1 of lymphosarcoma (leukosarcoma). We are including melanoma within this group of sarcomas notwithstanding the controversy as to whether these growths are of epithelial or of mesoblastic origin.

INCIDENCE

Sarcoma of the rectum, though well recognized and described, occurs infrequently. It has been estimated that only 0.5 per cent of all rectal neoplasms are sarcoma. Weeks [1] estimated that 1 of each 242 sarcomas occurred in the rectum, Williams (quoted by Pennington [2]) 1 in 270 and Lapeyre [3] 1 in 216. Sarcoma occurs with less frequency in the rectum than in other portions of the gastro-intestinal tract. Pennington [2] quoted Corner-Fairbanks that of 175 gastro-intestinal sarcomas only 11 were in the large bowel, 7 of these being in the rectum. These figures undoubtedly include melanotic tumors, which, according to Weeks,[1] "are twice as frequent as other sarcomas of the rectum."

The literature contains relatively few case reports. Weeks [1] stated that "approximately 100 cases are to be found in the literature, and that if doubtful cases were excluded the number would be reduced one-half." Quénu and Hartmann [4] gathered 20 cases in 1899. Bonnett and Chalier [5] reviewed 54 cases in 1911. Lapeyre [3] collected 30 cases (adding 2 personal ones) in 1920. With these exceptions, most of the articles have

1. Weeks, J. H.: Sarcoma of the Rectum, Surg., Gynec. & Obst. 44:478, 1927.

2. Pennington, J. R.: A Treatise on the Diseases and Injuries of the Rectum, Anus and Pelvic Colon, Philadelphia, P. Blakiston's Son & Company, 1923, p. 505.

3. Lapeyre, N. C.: Le sarcome primitif du rectum, Rev. de chir. 58:223 and 487, 1920.

4. Quénu, E., and Hartmann, H.: Chirurgie du rectum, Paris, G. Steinheil, 1899.

5. Bonnett, P., and Chalier, A.: Mélanose généralisé à point de depart anorectal, Lyon méd. 116:917, 1911.

reported single cases, with a more or less general review.[6] Textbooks on proctology rarely mention more than 1 or 2 cases personally observed.

Thompson [7] in 1924 reported 4 cases of sarcoma of the rectum studied at the Mayo Clinic. These represented all such growths seen there up to that time.

Concerning pathologic grouping, Lapeyre [3] divided his 30 cases into: 13 round cell sarcomas, 12 spindle cell sarcomas, 2 lymphosarcomas, 2 myosarcomas and 1 osteosarcoma.

Pennington [2] listed 60 rectal sarcomas as follows: 25 round cell sarcomas, 21 spindle cell sarcomas, 8 lymphosarcomas, 2 myosarcomas, 2 fibrosarcomas, 1 alveolarsarcoma and 1 ossifying sarcoma.

REPORT OF CASES

CASE 1.—*History.*—G. H., a white man, aged 47, a laborer, first seen on April 28, 1931, was referred by the urologic department of the Detroit City Physicians' Office to the proctologic clinic because of a mass in the rectum noted on routine genito-urinary examination. The illness had begun with pain two months before, which seemed to radiate into the penis. It had originated with rectal distress, which had given place for the past month to urogenital pain, which was worse at night. There was no burning on urination or bleeding. When pain in the penis was severe, there was also pain over the left sacral region. Bowel movement was not distressing, nor was there any rectal bleeding. A year and a half ago, the patient had had a painful swelling at the margin of the anus, which subsided spontaneously (probably thrombotic hemorrhoid).

Examination.—On rectal examination, a rounded swelling about 1 inch (2.5 cm.) in diameter was found immediately to the left of the prostate. It was smooth and firm but not stony hard, and very tender on deep palpation. It was somewhat movable underneath the rectal mucosa, projecting into the rectum like a polyp with a wide base. There was no ulceration over the mass.

The patient was admitted to St. Mary's Hospital, and operation was performed on May 5 by one of us (Dr. Kallet).

Operation.—There was a rounded tumor in the left rectal wall lying beneath the mucosa between the sphincter and the prostate. The mass was dissected free and was shelled out in many fleshy particles having the appearance of the inspissated contents of a sebaceous cyst.

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6. (a) Saphir, J. F.: Large Spindle Celled Sarcoma of the Rectum, New York M. J. **110**:798 (Nov. 15) 1919. (b) Whiteford, C. H.: Sarcoma of the Rectum, J. Path. & Bact. **15**:293, 1910. (c) Stimson, C. A.: Spindle Cell Sarcoma of the Rectum, Tr. Am. Proct. Soc., 1927, p. 7. (d) Churchman, J. W.: Melanosarcoma of the Rectum, with Report of a Case, Am. J. M. Sc. **155**:639 (May) 1918. (e) Kraker, D. A.: Melanosarcoma of the Rectum; Report of a Case, Am. J. Surg. **38**:271, 1924. (f) Allen, Victor K.: Melanotic Carcinoma of the Anus, Tr. Am. Proct. Soc., 1931, p. 31. (g) Hertzler, A. E.: Perirectal Melanoblastoma Developing in Cutaneous Hemorrhoid, S. Clin. North America **3**:1493 (Dec.) 1923.

7. Thompson, J. W.: Sarcoma of the Rectum, Proc. Staff Meet., Mayo Clin. **2**:241 (Oct. 5) 1927.

The pathologic report was made on May 7 by Dr. J. E. Davis. The mass was described as a soft, velvety, new growth. One section showed connective tissue types of cells arranged in whorls. The cells were not anaplastic, and were very regular. In another section the cells were anaplastic and irregular, almost replacing normal tissue; there were a few giant forms. All of the tissue was highly
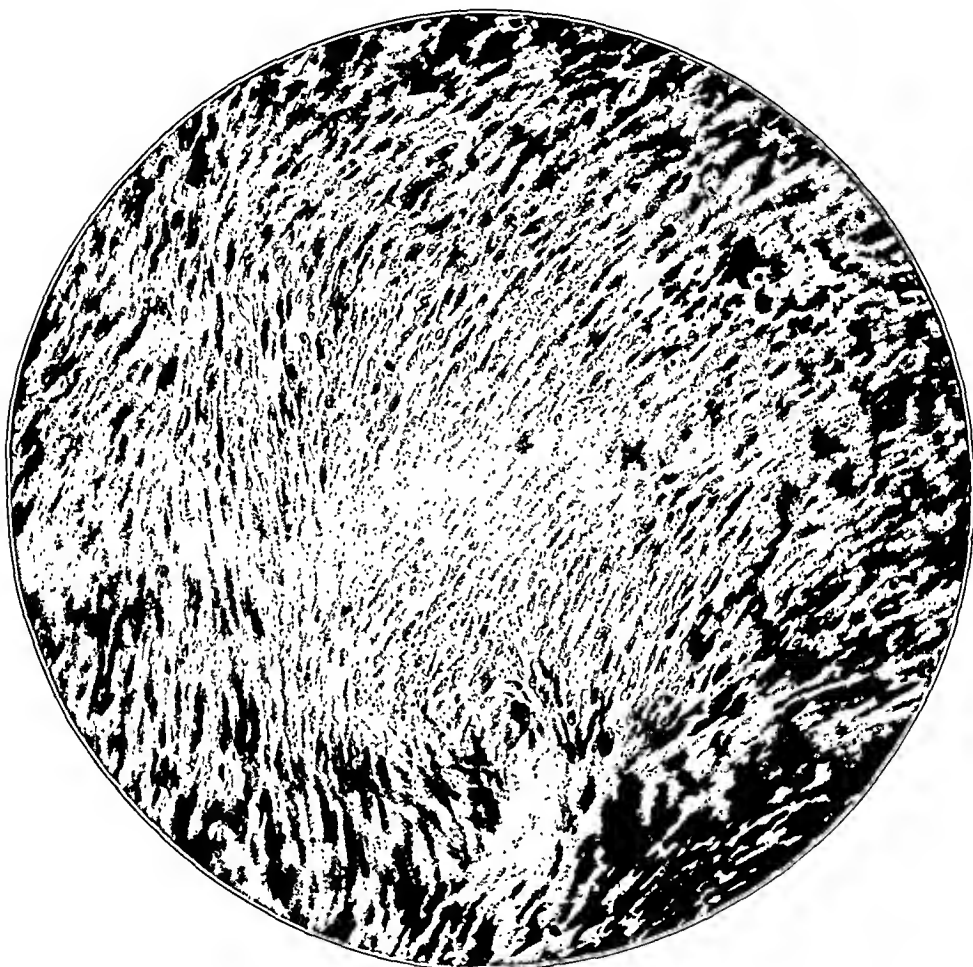
Fig. 1 (case 1).—Spindle cell sarcoma.

cellular; there was no differentiation initiating any specific process. The diagnosis was spindle cell sarcoma of the rectum in midripe stage, grade 1 radiosensitivity, grade 3 malignancy.

Course.—On May 14, four radon seeds of 1 millicurie were implanted surrounding the growth. Intensive deep roentgen therapy was given subsequently.

On May 23, the patient was discharged. When again seen on November 1, the mass had disappeared, and he felt well. On December 11, he was in excellent health, and at the time of writing there has been no local recurrence.

CASE 2.—*History.*—M. F., a white youth, aged 17, a university student, was admitted to Harper Hospital on Feb. 14, 1931, to Dr. Kallet's service. His present illness had begun six weeks before, with pain on defecation, radiating down the left leg like sciatica. This had become increasingly severe, so that he could not sleep, and a diagnosis of osteomyelitis of the hip had been considered. The family history showed that the father had died of carcinoma of the rectum at a rather early age.
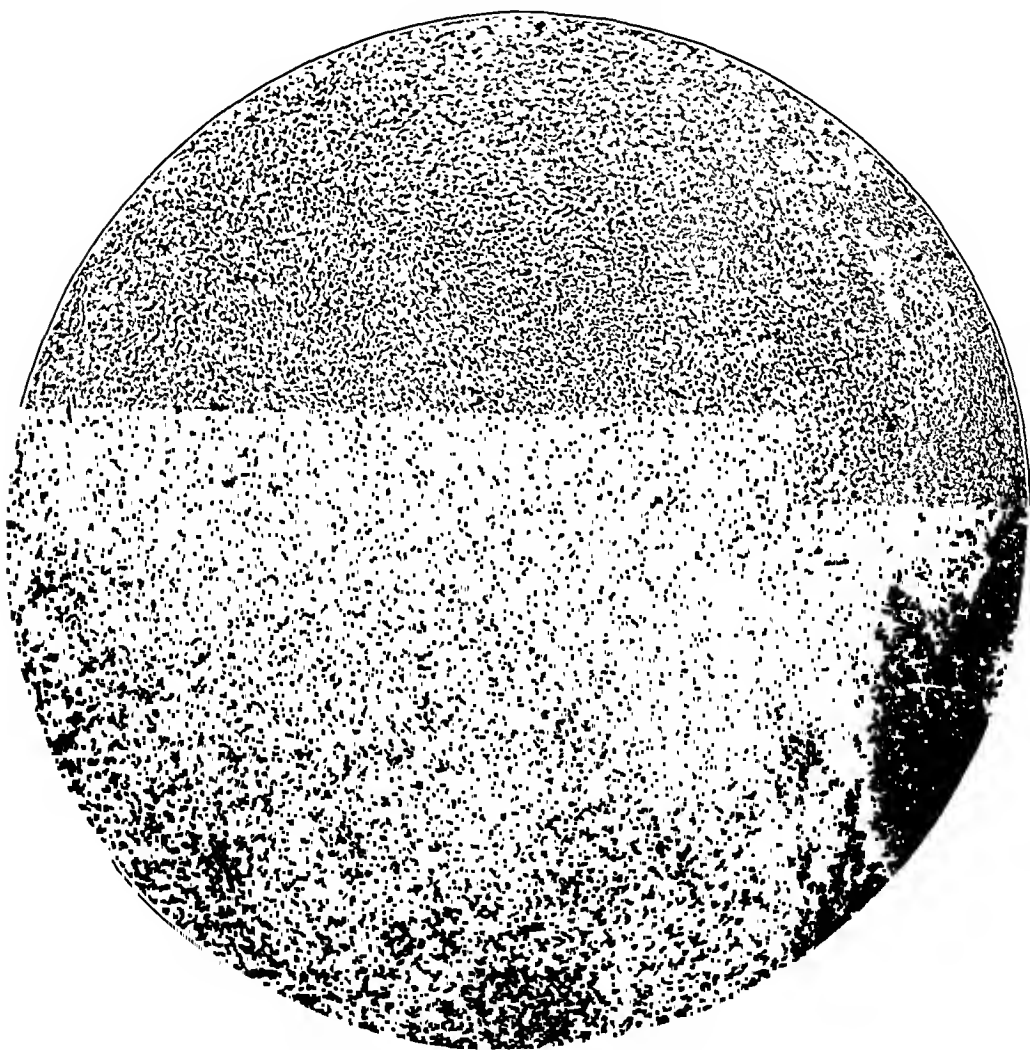
Fig. 2 (case 2).—Spindle cell sarcoma.

Examination.—Examination showed a young man of good nutrition apparently not acutely ill. On rectal examination, a mass about the size of a hen's egg could be felt beneath the mucosa of the anterior rectal wall overlying the region of the left seminal vesicle. The mass was fluctuant and somewhat tender. The prostate was normal.

Operation.—On the day of admission an incision was made by one of us (Dr. Kallet) through the anal mucosa into the mass. It lay deep in the presacral region,

was firm like a neoplasm and covered with rectal mucosa. Several ounces of grumous bloody fluid containing particles of tumor tissue were evacuated.

Microscopic examination was made by Dr. P. F. Morse, who diagnosed the mass as a spindle cell sarcoma of a very malignant type.

Course.—Following his discharge from the hospital, the patient consulted Dr. G. E. Pfahler in Philadelphia. There intensive deep roentgen therapy and radium needle implantation were given. The tumor proved unresponsive to this treatment. On May 15, he returned to Detroit. At that time there were marked cachexia and
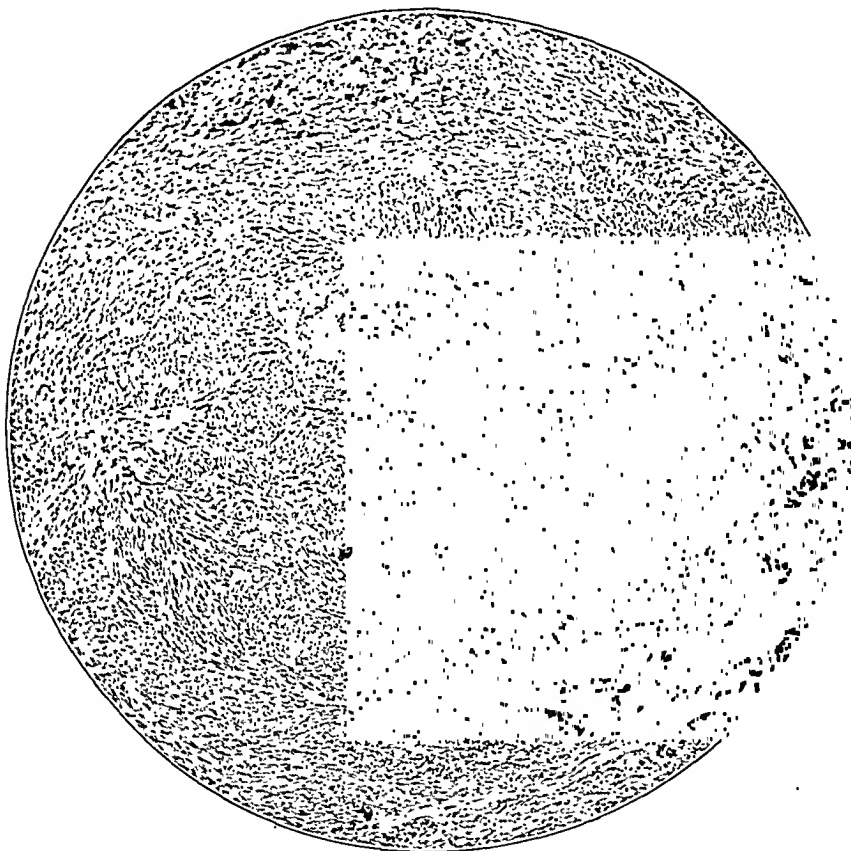
Fig. 3 (case 3).—Myosarcoma. Section from peripheral portion of tumor. Other areas showed marked anaplasia.

excruciating pain. There was a large sloughing mass in the rectum which practically occluded the lumen. Colostomy was recommended, and the patient entered the University Hospital at Ann Arbor. There a cordotomy was performed (May 21), followed shortly by a colostomy (June 9). The patient was relieved from pain until his death, which occurred on June 22.

CASE 3.—*History.*—A. T., a man, aged 46, first seen on Feb. 8, 1927, in the proctologic clinic, Detroit City Physicians' Office, complained of severe constipation and rectal protrusion. For several years he had had infrequent stools and had taken Sal Hepatica every two or three days. Three months before, a small, hard mass protruded on defecation, returning spontaneously. Since then the stools

had been soft like butter, but there was no diarrhea. Bowel movement had been growing more difficult, and on straining, the patient had had a sensation as if a mass like an egg were crowding into the anus. Sometimes this mass protruded. There was little pain.

Examination.—Examination showed a well developed man in good nutrition. A hard mass was felt externally to the right side of the anus. The sphincter was spastic. On digital exploration, beginning about three fourths of an inch (1.9 cm.) above the anus, a large, hard mass was felt extending to the right and bulging into the rectum. The upper limit of the mass could not be palpated. A deep trough was felt on either side of the mass where it joined the rectum. The tumor seemed to fill the entire presacral space and encroached so on the lumen of the rectum as practically to close it. The mucosa over the tumor appeared intact.

The patient was referred to the Detroit Receiving Hospital, and was admitted to the service of Dr. L. J. Hirschman on February 9.

Operation.—On the day following admission, operation was performed by Dr. Hirschman. A three and one-half inch (8.9 cm.) incision was made, beginning at the outer margin of the external sphincter. The incision was carried into the gluteal area until the mass was reached. This was freed from surrounding tissues by blunt dissection. The portion adherent to the upper surface of the rectum was clamped and cut away, thus removing a small area of rectal tissue. A large iodoform pack was used.

Pathologic examination was made by Dr. O. A. Brines. The specimen weighed 1,400 Gm. and measured 12 cm. in diameter. Microscopic examination showed a new growth of smooth muscle arranged in interlacing bundles and containing a moderate amount of fibrous tissue. A section from the central portion of the tumor showed conspicuously immature cells with marked anaplasia. Another section from the periphery showed all mature cells of leiomyoma. The diagnosis was myosarcoma of the rectum.

Course.—There was improvement following the patient's discharge from the hospital. Constipation was relieved, and there was gain in weight. Within two months, however, a yellowish purulent discharge developed from the rectum, with some bleeding. Constipation recurred, with loss of strength.

On September 23, the patient was readmitted to the Detroit Receiving Hospital. Rectal examination showed a long, irregular scar posteriorly. An irregular mass was palpable on digital exploration, almost filling the rectum.

On October 12, a midline colostomy was performed, and the patient was referred for deep roentgen therapy.

On Jan. 30, 1928, the rectal mass was increasing in size, and the patient had an irregular septic temperature.

On March 10, a raw mass larger than a fist obscured the anal canal. It was covered with whitish exudate and had eroded into the left buttock. It looked like raw meat and had a foul odor.

Severe hemorrhage occurred, with death on March 11.

CASE 4.—*History.*—Mrs. A. B., aged 47, was admitted to the Harper Hospital on June 18, 1920, to the service of Dr. Angus McLean, with the complaint of severe vaginal and rectal discharge since the last menses three weeks before, and protrusion from the rectum at defecation.

Operation.—On July 5, local resection was made of a gangrenous rectal polyp, with curettement of the base.

The pathologic report was made by Dr. P. F. Morse, who returned a diagnosis of very malignant melanosarcoma of the rectum.

Course.—The patient made a good recovery and was symptom-free for four years. At that time signs of localized intracranial pressure developed, and she died one year later. There was no local recurrence of the original mass.

CASE 5.—*History.*—Mrs. M. A., aged 58, a housewife, consulted one of us (Dr. Kallet) on June 21, 1931, with the history of a sudden attack of constipation and rectal pain two months before that had not been aggravated by bowel movement.
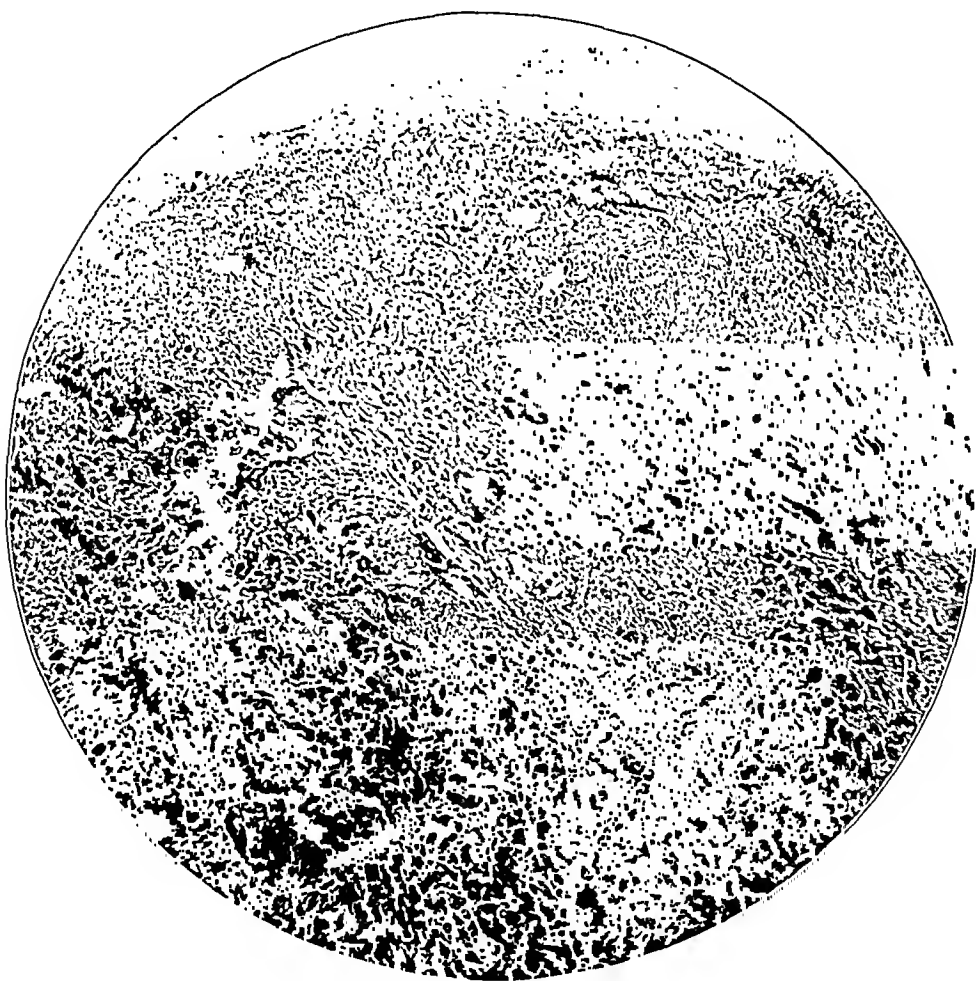
Fig. 4 (case 4).—Highly pigmented melanoma.

Two weeks later she began to notice bright red blood in the stools. Since that time she had required mineral oil in large quantities. Bowel movements were small and in thin pieces. She had lost 13 pounds (5.9 Kg.) in two months. She had had a hysterectomy nine years before. She complained of severe hemorrhages from puberty to the menopause.

Examination.—The rectum externally was normal. There was a hard, nodular mass on the right side of the rectum, located 1 inch (2.5 cm.) above the sphincter, reaching into the anal canal and involving the right side of the rectovaginal septum.
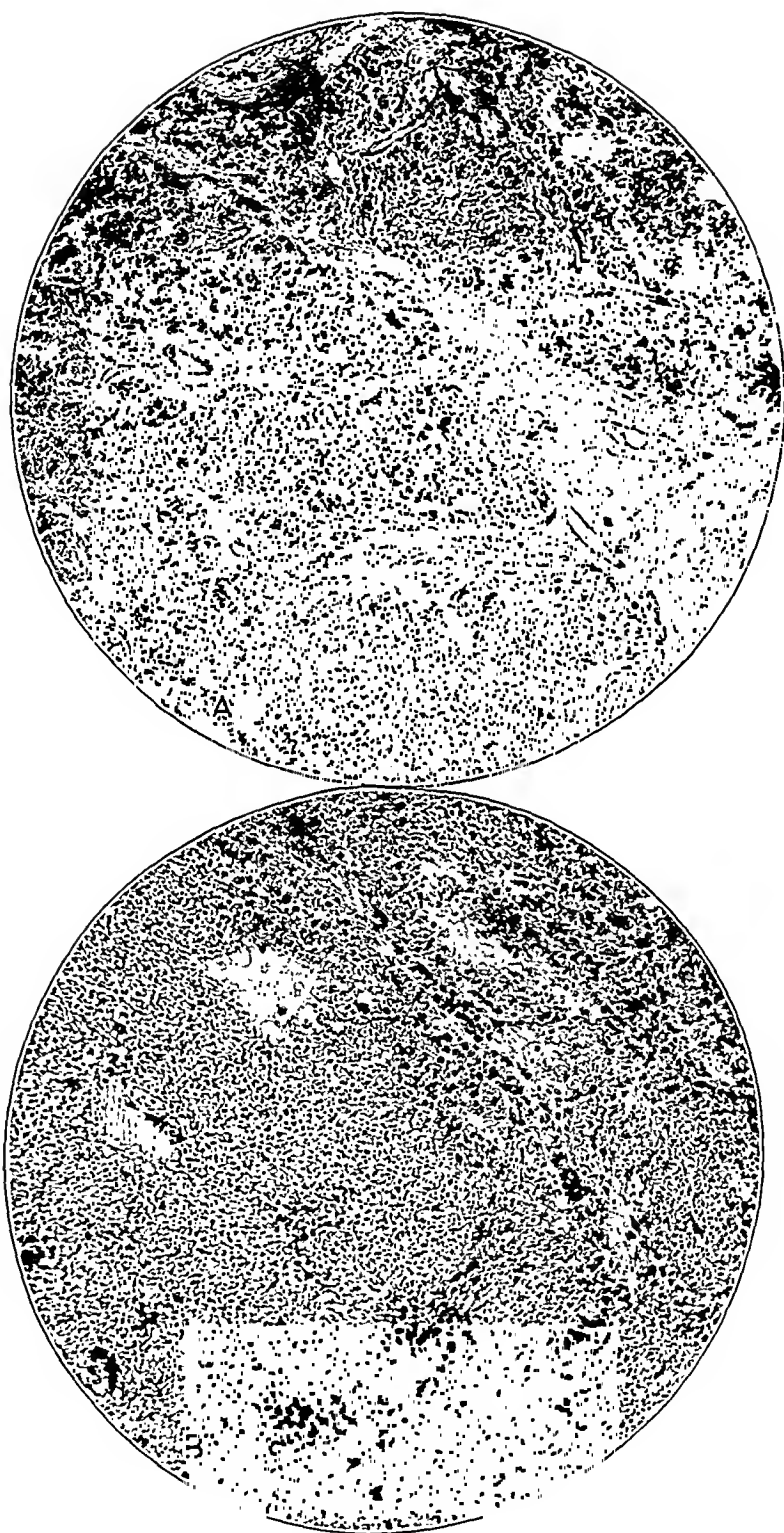
Fig. 5 (case 5).—Cellular melanoma. *A* shows the early lesion with alveolar round cell arrangement and very little pigment; B shows marked pigmentation (metastatic growth).

The growth was about 2 inches (5 cm.) in diameter, well defined and slightly ulcerated. The patient was referred to Harper Hospital on June 22, and was admitted to the service of Dr. L. J. Hirschman.

Operation.—On June 26, Dr. Hirschman made a perineal extirpation of the rectum. The growth, with a portion of the posterior vaginal wall, was excised. The resection was carried up to the sigmoid; the sigmoid end was brought down and
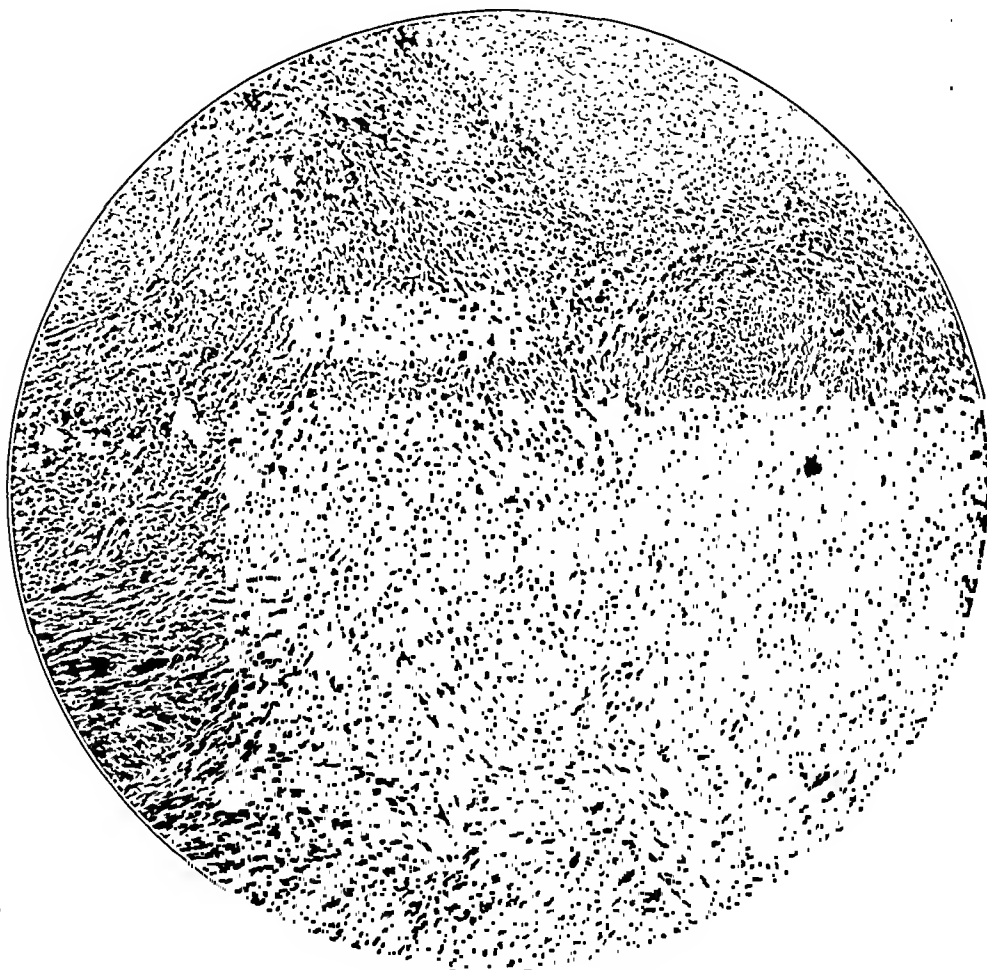
Fig. 6 (case 6).—Melanoma. Note the spindle cell arrangement.

sutured to the skin of the anus, preserving the sphincter. The rectovaginal septum was repaired with interrupted catgut stitches.

The pathologic diagnosis was melanosarcoma. The melanin was very scant.

Course.—Within a week, a rectovaginal fistula developed. Two attempts were made to repair this. About October 1, a hard visible mass about the size of a cherry developed in the right inguinal region. At the same time, a hard ulcerated mass, 1½ inches (3.8 cm.) in diameter, was noted to the left of the anal orifice. Biopsy of tissue from both of these masses showed advanced metastatic melanosarcoma. Both masses were deeply pigmented and almost black. The patient was

severely anemic, and was given large doses of ventriculin. Deep roentgen treatment was instituted locally.

On Jan. 4, 1932, the patient was up and about. The anemia showed some improvement, but she was still extremely weak.

CASE 6.—*History.*—J. M., a white man, aged 61, a painter, was admitted to Harper Hospital, Dr. L. J. Hirschman's service, on March 23, 1928. His illness had begun about three years before with rectal protrusion and bleeding. Two years before he had been operated on by Dr. Hirschman for a large rectal neoplasm, which pathologically was melanosarcoma. The growth and postsacral glands were excised, and he improved for eighteen months. At that time, pus appeared in the stools, severe constipation was present, and defecation was painful. There was no bleeding. There had been a loss of 10 pounds (4.5 Kg.) in weight. Urination had become difficult, and there were recent incidents of acute retention.

Examination.—Examination showed a thin, somewhat emaciated man. Rectal examination showed melanotic spots on the skin around the anus. A polypoid mass presented on the posterior rectal wall. There was a hard, fixed mass on the anterior wall of the rectum, in which the prostate seemed included.

Operation.—At operation on March 24, Dr. Hirschman found a growth the size of a child's head situated between the fundus of the bladder and the prostatic and pelvic floor. The sigmoid was densely adherent. The mass was removed with great difficulty through a transverse incision. A hypertrophied infected gland was removed posterior to the anal canal.

Microscopic examination showed a very malignant spindle cell melanosarcoma.

Course.—Postoperatively, there were hiccup, elevation of the temperature in the evening, pain in the lower part of the abdomen and retention of nitrogen. Death occurred on April 6, twelve days after operation.

CASE 7.—*History.*—J. M., a white man, aged 51, a laborer, was first seen by one of us (Dr. Kallet) on November 15, 1927. He was referred by Dr. Norman K. H'Amada, complaining of pain on defecation, tenesmus and bleeding from the rectum. Four weeks previously he had a chill and began to have pain in the buttocks. For the two following weeks he was extremely constipated, his bowel movements being pencil-like. Then the constipation was replaced by severe diarrhea. There were six or seven movements an hour. He passed considerable flatus, blood and mucus and had an apparent urge to move the bowels continuously. Each movement was accompanied by pain so severe as to be unbearable. He felt himself growing weak and stated that he had lost 7 inches (17.78 cm.) from his belt line.

Examination.—Examination disclosed a well developed and well nourished man of middle age, who was weak and somewhat pale. He appeared acutely ill. The teeth were carious, and the gums were in poor condition.

The cervical and axillary glands were slightly enlarged, and the inguinal glands were markedly enlarged. The abdomen was distended and generally tender. No masses were felt.

On digital examination of the rectum a mass could be felt which originated about 2 inches (5 cm.) above the anus and filled the entire ampulla. The lumen of the rectum was almost obliterated. The mass was annular, firm and tender. It gave the impression of being submucosal in origin.

Proctoscopic examination showed that the mucosa of the rectum seemed to be markedly congested and presented many petechial hemorrhages. No effort was made to pass the sigmoidoscope through the tumor.

Fig. 7 (case 7).—Lymphosarcoma (leukosarcoma). *A* shows lymphatic infiltration of pelvic cellular tissues; *B*, high power magnification.

Course.—The patient was admitted to Providence Hospital on November 17. The course in the hospital was rapidly downward. On admission there were a few petechial hemorrhages over the lower part of the abdomen and a few on the chest, although none had been noted at the first examination. Within the next two or three days, there were purpuric spots over the entire body. Four days after admission there was a slight oral hemorrhage. Some epistaxis, hematuria and bloody diarrhea (from eight to ten stools per hour) developed. The patient became extremely weak. The hemorrhages from all the body orifices increased, and the severe pain in the rectum required heavy doses of morphine for relief.

Dr. A. Kunin made an examination of the blood. Dr. W. L. Brosius' report on a smear was: "The large mononuclear cells of the lymphocytic group closely resemble the cells of the tumor."

The red blood cells numbered 4,900,000, and the hemoglobin was 75 per cent. The results of the differential counts were:

Date	White Blood Cells	Poly-morpho-nuclears, per Cent	Small Mono-nuclears, per Cent	Large Mono-nuclears, per Cent	Eosino-phils, per Cent
11/18/27	38,000	23	6	69	2
11/20/27	56,400	13	5	80	2
11/23/27	60,000	16	6	77	1

Emergency colostomy was performed for impending intestinal obstruction on November 26 by one of us (Dr. Kallet). Under local anesthesia the transverse colon was rapidly pulled into the abdominal wound, fixed and not opened.

Rapid abdominal exploration revealed no further masses.

Following operation there was a severe nosebleed, and the urine passed was practically pure blood. The patient died four hours later.

The pathologic report was made by Dr. Brosius. Local removal of a portion of the tumor post mortem showed microscopically an extensive infiltration of the rectal mucosa, muscle, fibrous layers and prostate gland. It was a solid tumor composed of uniform rounded cells with round, deep-staining, coarsely granular nuclei and a scanty amount of relatively clear cytoplasm essentially lymphoid, resembling the lymphocyte of the lymph node. Anaplasia was not very marked, but invasiveness was decidedly marked. Examination of the blood smear made on November 23, showed 77 per cent of large mononuclear cells of the lymphocytic group, which closely resembled the cells of the tumor.

The diagnosis was leukosarcoma of Sternberg.

COMMENT

The clinical manifestations and progress of these patients conform in general to the description found in most textbooks. However, certain points may merit emphasis.

Both sarcoma and melanotic growths arise beneath the mucosa, ordinarily either in the anal canal or in the lowest part of the ampulla. It is often stated that these growths generally originate in the posterior wall. However, six of our cases were on the anterior wall. When located anteriorly, the first symptoms may be due to pressure on the structures at the neck of the bladder. The patient in case 1 consulted a urologist for pain radiating into the penis. Case 6 presented involvement of the prostate and bladder wall.

In several of the histories, pain was a prominent early symptom. In case 1, as noted, it radiated to the penis. In case 2 it radiated along the left sciatic nerve and was so excruciating that the patient could not sleep. In case 4 there were terrific tenesmus and rectal spasm out of all proportion to that seen in early rectal cancer. The patient in case 5 also had severe rectal pain.

The first objective manifestation—the mass beneath the mucosa—is early of insignificant appearance and may be confused with a benign polyp or hemorrhoid. This emphasizes the importance of pathologic examination of all excised hemorrhoid tissue.

The mucosa remains intact as the early growth of the neoplasm proceeds. With straining at stool, the tumor frequently develops into a polyp, usually with a short pedicle which may protrude and recede painlessly on defecation. The first manifestation in case 3 was a small mass which was extruded with each bowel movement. In case 4 a bulging gangrenous rectal polyp proved to be melanoma.

More often the growth develops locally, forming a mass almost indistinguishable from carcinoma. In sarcoma the mucosa tends to remain intact longer, and ulceration occurs late. There is not the marked obstruction seen in some rectal cancers. Digital examination gives the impression that the lumen of the rectum is being compressed by an extra mucosal mass, whereas in carcinoma there is rather a sensation of direct involvement of the mucosa, with early crater formation. Occasionally sarcoma develops as a semifluctuant granulomatous mass which clinically invites incision for drainage. (When incision was made in case 2 a grumous, sanguineous fluid was discharged containing many fleshy particles).

Melanoma.—In our cases there was little distinguishable difference between the clinical course of melanoma and of sarcoma. As a matter of fact, even a histologic differentiation may be difficult, for melanomas tend to develop spindle cells, and at first their pigment may be absent or so scanty as to escape detection. The metastatic deposits, on the contrary, usually exhibit heavy pigmentation, as may older tumors. Case 5 showed very faint pigment granules, scarcely discernible in the first section, while the later metastases were densely pigmented.

The origin of these growths (melanotic) is at present a matter of controversy. Several proctologists and many dermatologists classify them as of epithelial derivation—melanocarcinomas. However, Ewing,[8] in a careful critical review, considers that Soldan and more recently Masson have proved more or less conclusively that the original melanoma cell is of mesoblastic or neuro-ectodermal, certainly not epithelial, origin. He believes that the nevus cell is derived from and belongs to the

8. Ewing, James: Problems in Melanoma, Brit. M. J. 2:852 (Nov. 22) 1930.

peripheral sensory nerve end apparatus. These pigment-bearing cells may and often do enjoy a more or less independent existence, and while they are more numerous in regions where the tactile sense is highly developed, such as the nail-bed, anus or orbit, they may be found in the skin or mucous membrane of any portion of the body.

Leukosarcoma.—The lymphatic neoplasm (case 7), on the other hand, was a distinct clinical entity: a rapidly fatal blood dyscrasia with hemorrhages from all mucous membranes, a steadily rising white cell count characteristic of lymphatic leukemia and a large lymphomatous mass surrounding the rectum. Sternberg has applied the term leukosarcoma to this condition. He differentiates three grades of lymphatic malignancy: (1) lymphatic leukemia as classically described, with a characteristic blood picture; (2) lymphosarcoma, a lymphomatous tumor without the leukemic blood picture, and (3) leukosarcoma, a local malignant lymphomatous tumor with the blood picture of lymphatic leukemia.

There is considerable objection among some pathologists, Ewing, Herxheimer and others, to the separation of these tumors into a special group. They contend that the majority of these growths represent only an excessive hyperplasia of the lymphoid tissue such as is observed in lymphatic leukemia.[9] However, the term is still used. In our case, although there was a definite mass constricting the lumen of the rectum, the microscopic picture was more nearly that of a leukemic infiltration of the pelvic cellular tissues.

Leukosarcoma has been described in various locations, including the gastro-intestinal tract. Warthin reported its occurrence in the ileum, and Moritz in the cecum. Weiss[9] has also described it in the cecum. We have been unable to find a similar rectal neoplasm on record.[10]

Prognosis.—Most authors state that sarcoma and melanoma of the rectum are invariably fatal. Very few patients have survived more than two years following any treatment. It has been noted that sarcomas of the rectum do not spread locally as carcinomas do. There is a rapid extension to the inguinal nodes and then to the liver, lungs and other viscera. Most authors recommend wide radical resection. Churchman[6d] has advised preliminary laparotomy before extensive resections are undertaken to determine the presence of abdominal metastasis, which he believes will be found in 80 per cent of the cases.

Radium and roentgen therapy have been used both alone and in combination with surgical measures, but their value is as yet not definitely established. So far as we have been able to determine, no cures have been reported.

9. Weiss, Emil A.: Case of Localized Leucosarcomatosis of the Ascending Colon and of the Cecum. J. Lab. & Clin. Med. **16**:567 (March) 1931.

10. Flashman, David H., and Leopold, Simon S.: Leukosarcoma, Am. J. M. Sc. **177**:651, 1929.

The results of our series were as follows:

Case 1, spindle cell sarcoma: The patient is well and free from recurrence eight months after local resection, implantation of radon seeds and deep roentgen therapy.

Case 2, spindle cell sarcoma: There was a rapidly downward course, with death in four months, despite local removal and intensive radiation.

Case 3, myosarcoma: The course was progressively downward despite operation and deep roentgen therapy, death occurring thirteen months after local resection.

Case 4, melanoma: The patient was symptom-free for four years after local removal. Death occurred five years post operatively, following cerebral symptoms, perhaps metatases. There was no local recurrence.

Case 5, melanoma: The patient is alive seven months after resection and deep therapy, but is rapidly failing.

Case 6, melanoma: There was improvement for eighteen months following local resection. Death occurred two months later, following operation for recurrence.

Case 7, leukosarcoma: The patient died six weeks from the onset, with symptoms of acute lymphatic leukemia.

SUMMARY

1. Seven cases of unusual rectal tumors, three sarcomas, three melanomas and one leukosarcoma, are reported.

2. The clinical features and course of these neoplasms are discussed.

EXPERIMENTAL THYROID HYPERPLASIA

AN INCREASED INTAKE OF CHLORIDE COMBINED WITH A DIET DEFICIENT IN IODINE AS A FACTOR

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At the present time endemic goiter is commonly placed in the category of a deficiency disorder, and attention is being focused on iodine as the lacking element. This is a natural tendency because of its apparent therapeutic value. Hellwig[1] opposed this point of view and stated that a positive factor and not a deficiency of iodine is the essential cause. He believes that an increased intake of calcium chloride represents a positive agent, and if combined with a deficiency of iodine hyperplasia of the thyroid will result.

My purpose in this paper is to report an experimental study on thyroid hyperplasia produced in a relatively nonendemic region based on the theory that calcium chloride represents a positive factor.

REVIEW OF THE LITERATURE

Knappenburg,[2] in 1919, reported negative results in a series of rats fed on water containing but a small amount of iodine. His experiments were conducted in Holland, a goiter-free region, the water being supplied from an endemic area. A year later, Houssay[3] conducted a similar experiment in Buenos Aires, another nongoitrous region, and stated that goiter developed in only two rats, from several lots of twenty each, when supplied by water from a goitrous region. McClendon[4] discounted this work, saying that the iodine content of the food was not determined. In 1922, McClendon and Williams,[5] working in Minne-

1. Hellwig, C. A.: Iodine Deficiency and Goiter, Arch. Path. **11**:709 (May) 1931.

2. Knappenburg, B. D. G.: Geneesk. bl. u. klin. en lab. v. d. prakt. **21**:300, 1919; quoted by McClendon (footnote 4).

3. Houssay, B. A.: Rev. d. Inst. bact. **2**:629, 1920; quoted by McClendon (footnote 4).

4. McClendon, J. F.: Distribution of Iodine with Reference to Goiter, Physiol. Rev. **7**:189 (April) 1927.

5. McClendon, J. F., and Williams, Agnes: Experimental Goiter and Iodine in Natural Waters in Relation to Distribution of Goiter, Proc. Soc. Exper. Biol. & Med. **20**:286, 1922-1923.

sota, an endemic area, produced changes in the thyroid gland in rats fed on a diet containing ten parts of iodine per billion parts of dry food. Hayden, Wenner and Rucker,[6] working in the same area, confirmed their results by producing thyroids twice the normal size in rats fed on a similar diet. Tanabe,[7] in southern Germany, also obtained hyperplasia in the thyroids of rats fed on a diet poor in iodine, but again, as Hellwig pointed out, "domesticated animals in goitrous areas incur goiters spontaneously."

Hellwig[1] failed to produce any changes in the thyroid gland in Kansas, a goiter-free area, when he used the same diet prescribed by Tanabe, and partially on these results he based his conclusions that the essential cause of goiter must be a positive agent rather than a deficiency of iodine alone. Orr's[8] extensive geological studies point to this conclusion. He studied the iodine content of the foodstuffs and soil in England and Scotland, and found no correlation between a deficiency of iodine in the food and the occurrence of endemic goiter. Wegelin[9] insisted that atrophy of the thyroid gland should result from a lessened intake of iodine since iodine stimulates the thyroid gland. Hellwig's experiments confirm this view, both grossly and microscopically. Following this assumption, he produced marked hyperplasia in rats' thyroids by using a diet high in calcium chloride and low in iodine. Hellwig[1] also wrote that Tanabe recently produced pronounced hyperplasia apparently from a diet high in calcium and low in iodine. Added evidence as to the value of calcium chloride as a positive agent is the work brought forth by McCarrison,[10] who, during a geological study of endemic goitrous areas in northern India, found that the drinking water was obtained from areas containing large deposits of limestone.

<div align="center">EXPERIMENTAL DATA</div>

Three groups of rats were studied in the first experiment. Group A received a normal diet, group B received a diet low in iodine, consisting of pearl barley, distilled water and 2 Gm. of raw beef every third day. Based on the diets used by Hellwig,[1] group C received barley, 2 Gm. of raw beef every third day and a 2 per cent solution of calcium chloride, instead of the distilled water. A determina-

6. Hayden, E. M.; Wenner, W. T., and Rucker, C. W.: Production of Goiter in Rats by Restricted Iodine Feedings, Proc. Soc. Exper. Biol. & Med. **21**:546, 1923-1924.

7. Tanabe: Experimenteller Beitrag zur Aetiologie des Kropfes, Beitr. z. path. Anat. u. z. allg. Path. **73**:415, 1925.

8. Orr, J. B.: Iodine Supply and the Incidence of Endemic Goiter, Medical Research Council Special Report Series, No. 154, London, His Majesty's Stationery Office, 1931.

9. Wegelin, quoted by Hellwig (footnote 1).

10. McCarrison, R.: The Thyroid Gland in Health and Disease, London, William Wood & Company, 1917.

tion of the iodine, made by Dr. Roe Remington,[10a] in the barley used in all experiments showed thirteen parts per billion. The housing of the rats during the experiment consisted of heavy mesh wire cages, with a raised floor and no bedding. The drinking water was contained in special drinking flasks to prevent contamination. The animals were killed on the one hundred and twelfth day, and the thyroids were dissected, weighed and sectioned for microscopic study. From table 1 and 2, it is evident that the thyroids in group B weighed much less than those in group A, both absolutely and in comparison with the body weight. Microscopically (fig. 2), they showed very abundant and deeply staining colloid, low epithelium and moderately small acini. This is in contradistinction to the pathologic picture of early mammalian goiter, which was described by Langhans and Wegelin,[11] Marine and Lenhart [12] and Hellwig [1] as showing extremely
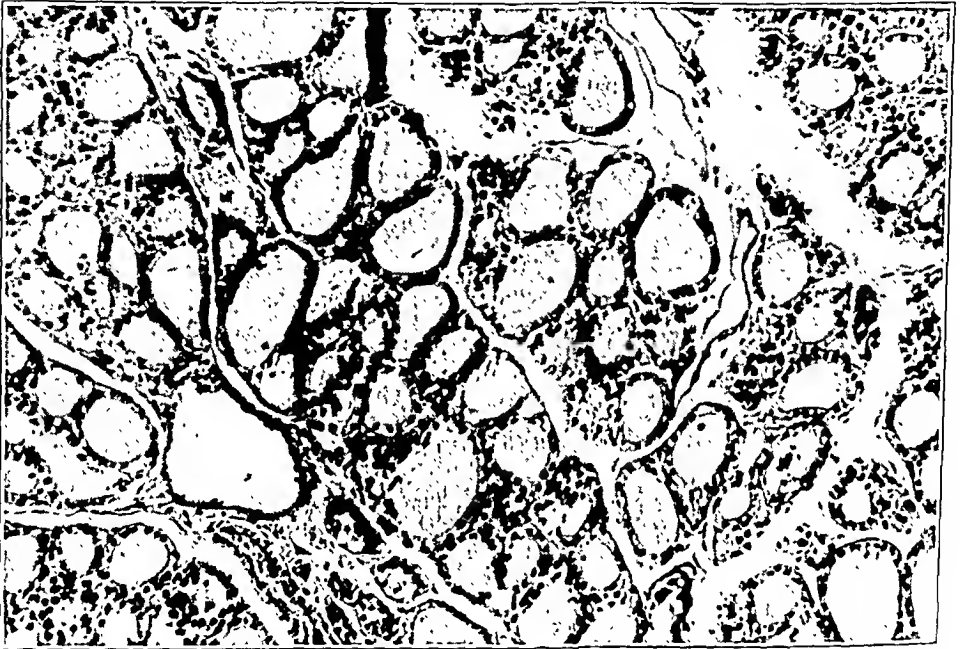
Fig. 1.—Normal thyroid of a rat grown in a relatively nonendemic region, New York.

small acini, a marked decrease in colloid, columnar epithelium with plications and papillae, mitotic figures and hyperemia of the gland. The results in group B correspond with Hellwig's work and also substantiate Wegelin's theory.[9] From a comparison of group C (table 3) and group B (table 2), it is obvious that the glands produced on the diet low in iodine and high in calcium chloride are much larger. In comparison with the normal, although the thyroids in group C are only slightly heavier absolutely, they are moderately greater when compared with

10a. Remington, Roe E.: Personal communication.

11. Langhans and Wegelin: Der Kropf der weissen Ratte, Bern, Paul Haupt Ackademische Buchhandlung, 1919; quoted by Hellwig (footnote 1).

12. Marine, D., and Lenhart, C. H.: Relation of Iodine to the Structure of Human Thyroids, Arch. Int. Med. 4:440 (Nov.) 1909.

the body weight. Five of the nine rats showed a definite hyperplasia of the thyroid gland as evidenced by the small size and irregularity of the acini, decrease in the colloid, high cuboidal or columnar epithelium with plications, numerous areas of solid cells, some desquamation and hyperemia (fig. 3).

TABLE 1.—*Group A, Normal Diet*

Rat No.	Weight, Gm.	Sex	Thyroid Weight, Mg.	Acini	Epithelium	Colloid*	Hyper-emia*	Hyper-plasia*
A-1	200	M	18	Large and moderate size	Flat and low cuboidal	3	0	0
A-2	201	M	30	Large and moderate size	Low cuboidal	3	1	0
A-3	209	M	20	Large and moderate size	Flat and low cuboidal	3	0	0
A-4	255	M	20	Large and moderate size	Flat and low cuboidal	3	1	0
A-5	166	M	31	Moderate size	Flat	3	0	0
A-6	204	M	40	Large size	Flat and low cuboidal	3	0	0

* In this and the following tables, colloid, hyperemia and hyperplasia are graded as follows: 0, none; 1, slight; 2, moderate, and 3, marked.

TABLE 2.—*Group B, Diet Low in Iodine With 3 Gm. of Beef Every Third Day*

Rat No.	Weight, Gm.	Sex	Thyroid Weight, Mg.	Acini	Epithelium	Colloid	Hyper-emia	Hyper-plasia
B-1	209	M	16	Moderate and small size	Flat and low cuboidal	3	0	0
B-2	204	M	15	Moderate and small size	Flat and low cuboidal	3	0	0
B-3	164	M	16	Moderate and small size	Flat	3	0	0
B-4	150	M	15	Moderate size	Flat	3	0	0
B-5	133	M	22	Moderate and small size	Flat	3	0	0

TABLE 3.—*Group C, Diet Low in Iodine and High in Calcium Chloride With 3 Gm. of Beef Every Third Day*

Rat No.	Weight, Gm.	Sex	Thyroid Weight, Mg.	Acini	Epithelium	Colloid	Hyper-emia	Hyper-plasia
C-1	168	M	25	Very small; solid areas	Cuboidal with budding	1	2	2
C-2	179	M	35	Very small; solid areas	Cuboidal, budding, papillae	1	2	2
C-3	181	M	36	Large and moderate size	Flat	3	0	0
C-4	130	M	33	Very small; solid areas	High cuboidal	1	2	3
C-6	194	M	39	Moderate size	Cuboidal and budding	2	1	1
C-7	146	M	23	Small; solid areas	High cuboidal	1	2	3
C-8	169	M	24	Moderate size	Flat and low cuboidal	3	0	0
C-9	223	M	40	Moderate size	Cuboidal	2	1	0
C-10	164	M	34	Moderate size	Cuboidal	3	0	0

The second experiment consisted of five more rats in group B, (table 4) and five more in group C (table 5). The diet was the same as in the preceding groups, except that the raw beef was withheld. The results obtained correspond exactly with those of the previous series, i. e., the rats on the diet low in iodine showed no thyroid hyperplasia, whereas the group on the diet low in iodine and high in
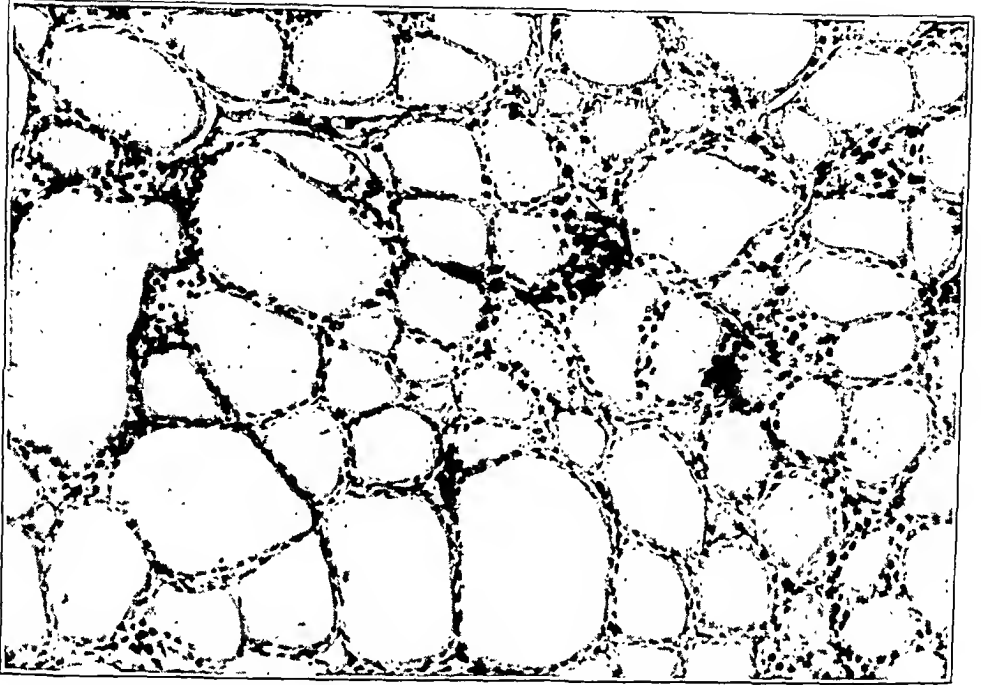
Fig. 2 (rat, B-8).—Thyroid after administration of a diet low in iodine for one hundred and twelve days.
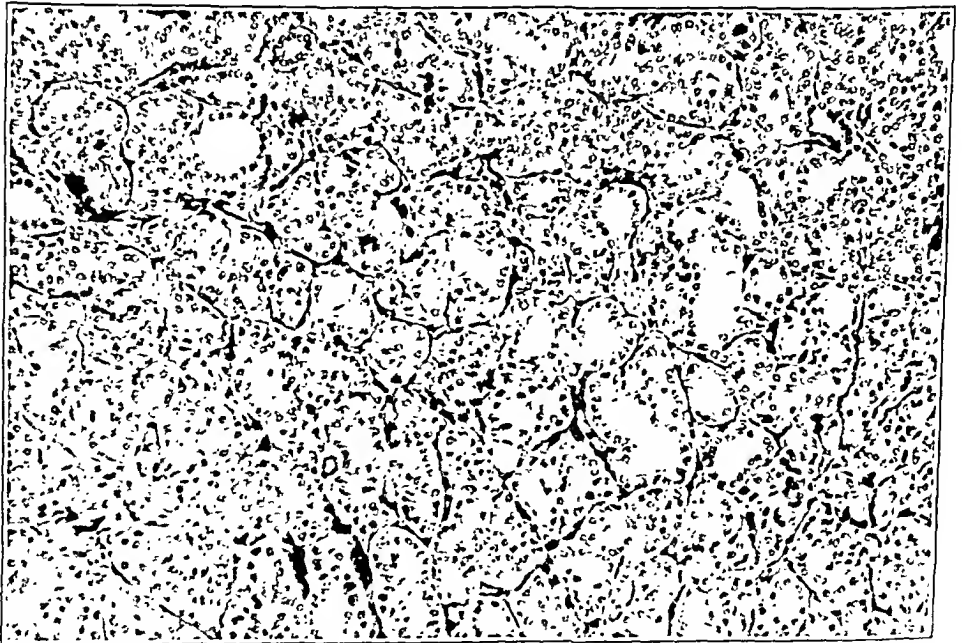
Fig. 3 (rat, C-23).—Thyroid hyperplasia produced by a diet low in iodine and high in calcium chloride.

calcium chloride showed definite changes. The results obtained in these experiments correspond closely with Hellwig's, although he was able to demonstrate more pronounced changes in his entire group.

Since ten of the fourteen animals showed definite hyperplasia on the diet high in calcium chloride and low in iodine it was thought advisable to run experiments on a larger group. Also, since the calcium was thought to be the active principle, it follows that hyperplasia would be produced even though a different calcium-containing ingredient was used. Conversely, changes would not be produced if the calcium ion was replaced. In accordance with these deductions, a third series of experiments was run. The same precautions were carried out as in the preceding series. The animals were allowed to live from ninety to one hundred

TABLE 4.—*Group B, Diet Low in Iodine*

Rat No.	Weight, Gm.	Sex	Thyroid Weight, Mg.	Acini	Epithelium	Colloid	Hyper-emia	Hyper-plasia
B- 6	162	M	16	Moderate and small size	Flat	3	0	0
B- 7	135	M	26	Moderate and small size	Flat and low cuboidal	3	0	0
B- 8	169	M	26	Moderate and large size	Flat	3	0	0
B- 9	126	M	18	Small size	Flat	3	0	0
B-10	132	M	20	Small and moderate size	Flat	3	0	0

TABLE 5.—*Group C, Diet Low in Iodine and High in Calcium Chloride*

Rat No.	Weight, Gm.	Sex	Thyroid Weight, Mg.	Acini	Epithelium	Colloid	Hyper-emia	Hyper-plasia
C-11	130	M	35	Very small and irregular	Cuboidal	1	3	2
C-12	120	M	28	Solid areas; irregular and very small	Cuboidal	1	2	2
C-13	132	M	32	Very small and irregular; solid areas, and areas showing no acinar form	Cuboidal	1	2	2
C-14	142	M	34	Same as for preceding animal	Cuboidal	1	3	2
C-15	138	M	29	Very small and irregular; solid areas	Cuboidal	1	3	2

and one days, after which their thyroids were dissected and sections made for microscopic study. Three groups of rats were distinguished in this series. Group C (table 6), twenty-nine more animals, received a diet low in iodine and high in calcium chloride. Twenty-two thyroids showed a definite hyperplasia, as shown in the previous group C.

Group D (table 7), twenty rats, received a diet consisting of pearl barley and a 5.4 per cent solution of calcium lactate, to serve as drinking water. The results were surprising, as none of the rats showed changes in the thyroid gland, although the calcium ion had been retained in the drinking water (fig. 4). Group E (table 8), sixteen animals, received a diet of pearl barley and a 3 per cent solution of sodium chloride. Likewise, the results obtained in this group were entirely unexpected. Definite hyperplasia, as demonstrated in figure 5, occurred in fifteen of the thyroids. The changes were very similar to the findings obtained in the group fed on a diet low in iodine and high in calcium chloride, although the calcium ion had been replaced by sodium.
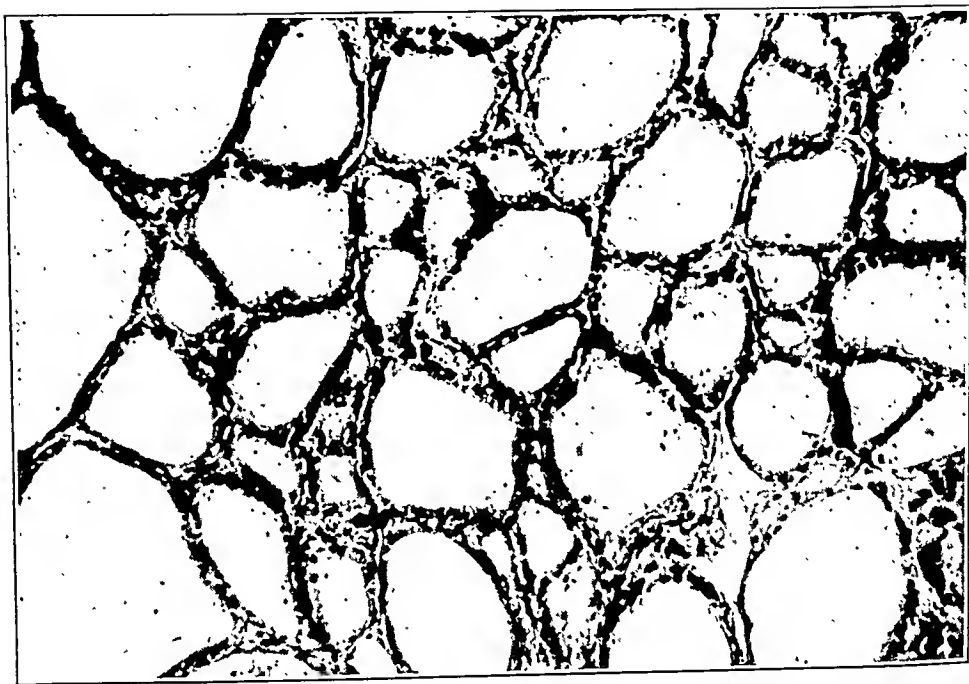
Fig. 4 (rat, D-18).—Normal thyroid after a diet low in iodine and high in calcium lactate.
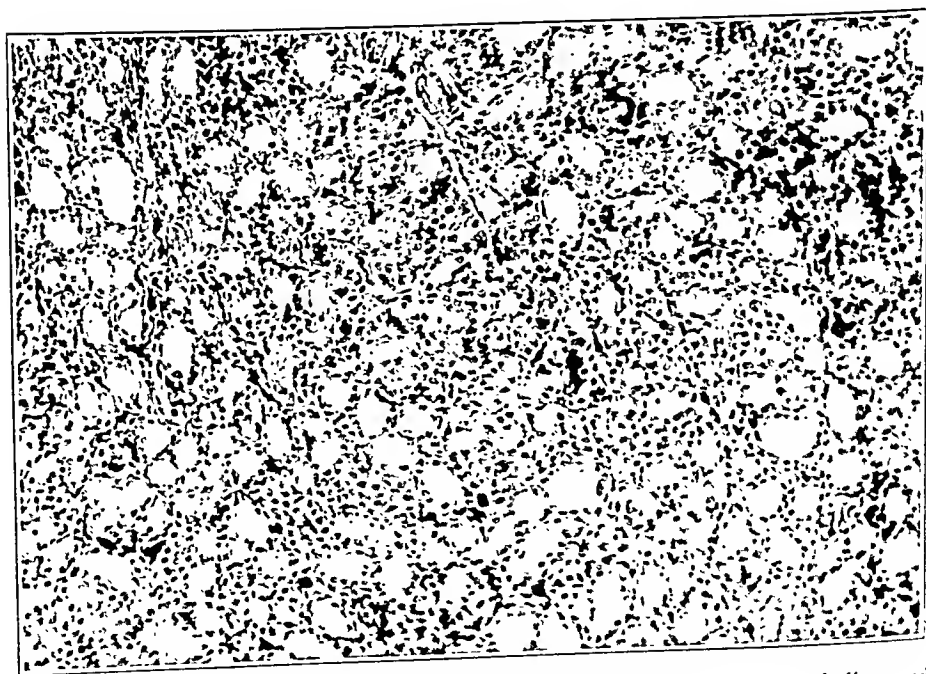
Fig. 5 (rat, E-16).—Thyroid hyperplasia produced by a diet low in iodine and high in sodium chloride.

TABLE 6.—*Group C, Diet Low in Iodine and High in Calcium Chloride*

Rat No.	Sex	Weight, Gm.	Acini	Epithelium	Colloid	Hyperemia	Hyperplasia
C-16	M	130	Very small; irregular and tubes	High cuboidal	1	3	2
C-17	F	135	Solid areas; very small and irregular	High cuboidal	1	3	2
C-18	M	140	Very small; many solid areas	High cuboidal and columnar	1	2	2
C-19	M	138	Moderate and small	Cuboidal	1	1	0
C-20	M	130	Small; tubes and solid areas	High cuboidal	1	2	2
C-21	M	135	Very small; tubes and solid areas	Columnar	1	2	3
C-22	M	140	Small, moderate; solid areas, buds	High cuboidal	1	3	2
C-23	M	150	Small; tubes, solid areas and buds	Cuboidal and columnar	1	3	3
C-24	M	170	Moderate and large size	Low cuboidal	2	1	0
C-25	M	180	Moderate and large size	Low cuboidal	2	1	0
C-26	M	120	Moderate and small size; budding	High cuboidal	2	3	1
C-27	F	120	Moderate, small; tubes, budding	High cuboidal	1	2	2
C-28	M	150	Moderate and small size	Cuboidal	2	1	0
C-29	M	150	Moderate and small; budding	Cuboidal	1	2	1
C-31	M	130	Large size	Flat	3	0	0
C-32	M	140	Small and irregular; solid areas	High cuboidal	1	3	2
C-33	F	120	Moderate, small and irregular	Cuboidal	1	3	1
C-34	F	135	Small and irregular	High cuboidal	1	3	2
C-35	F	115	Small size	High cuboidal	2	2	1
C-36	F	140	Moderate and irregular	Cuboidal	1	1	0
C-37	M	120	Small, moderate, irregular; solid areas	High cuboidal	1	2	2
C-38	F	102	Small, moderate, irregular; solid areas	High cuboidal; budding	1	2	2
C-39	M	150	Moderate, irregular; tubes, solid areas	High cuboidal	1	2	2
C-40	F	125	Moderate, small and irregular	High cuboidal	1	1	2
C-41	F	130	Large and moderate size	Cuboidal	2	2	0
C-42	F	125	Moderate; budding	Cuboidal	2	2	1
C-43	F	175	Moderate size	Cuboidal	2	2	1
C-44	F	135	Moderate and irregular size	High cuboidal	1	3	2
C-45	F	130	Moderate and irregular size	High cuboidal	1	3	2

TABLE 7.—*Group D, Diet Low in Iodine and High in Calcium Lactate*

Rat No.	Sex	Weight, Gm.	Acini	Epithelium	Colloid	Hyperemia	Hyperplasia
D- 1	M	98	Large and moderate size	Flat	3	0	0
D- 2	M	96	Large and moderate size	Flat	3	0	0
D- 3	M	140	Moderate; small tube forms, few solid areas	Flat and low cuboidal	2	2	1
D- 4	M	200	Moderate and large size	Flat and low cuboidal	2	1	1
D- 5	M	113	Large and moderate size	Flat	3	0	0
D- 6	M	140	Large and moderate size	Flat	3	0	0
D- 7	M	170	Large and moderate size	Flat	3	0	0
D- 8	M	150	Large and moderate size	Flat	3	0	0
D- 9	M	180	Large and moderate size	Flat	3	0	0
D-10	M	190	Moderate; few solid areas	Flat and low cuboidal	3	1	0
D-11	F	185	Large and moderate size	Flat	3	0	0
D-12	F	180	Large and moderate size	Flat	3	0	0
D-13	F	138	Large and moderate size	Flat	3	0	0
D-14	F	165	Moderate size	Flat and low cuboidal	3	1	0
D-15	F	140	Large and moderate size	Flat	2	0	0
D-16	M	210	Large and moderate size	Flat	2	0	0
D-17	F	210	Large and moderate size	Flat	2	0	0
D-18	F	160	Large and moderate size	Flat	2	0	0
D-19	F	210	Moderate size	Low cuboidal	2	1	0
D-20	F	160	Moderate size	Flat and low cuboidal	2	1	1

COMMENT

This experimental study agrees with the work of Hellwig [1] and the views of Wegelin [8] that thyroid hyperplasia is not due to a deficiency of iodine alone. McCarrison's [13] views that thyroid changes occur in animals when fed on a diet deficient in vitamins and leafy vegetables are not borne out. The study substantiates Hellwig's point of view that a positive factor is the essential cause, and when combined with a low iodine content may produce goiter. The experiments coincide with his results in that calcium chloride may act as a positive agent in producing goiter. Although there were definite changes in the thyroid glands in animals fed on a diet high in sodium chloride and low in

TABLE 8.—*Group E, Diet Low in Iodine and High in Sodium Chloride*

Rat No.	Sex	Weight, Gm.	Acini	Epithelium	Colloid	Hyperemia	Hyperplasia
E- 2	F	130	Small; tubes, solid areas, buds	Columnar and cuboidal	1	2	3
E- 3	M	140	Small; tubes, solid areas	High cuboidal	1	3	3
E- 4	F	150	Small; tubes, solid areas	High cuboidal	1	3	3
E- 5	F	130	Small; tubes, solid areas	High cuboidal	1	3	3
E- 6	F	120	Small; tubes, solid areas	Cuboidal	1	3	2
E- 7	M	132	Small; tubes, solid areas	High cuboidal and columnar	1	0	3
E- 9	F	125	Small; tubes, solid areas	High cuboidal	1	2	2
E-10	M	123	Small; tubes, solid areas	High cuboidal	1	2	3
E-11	M	128	Small; tubes, solid areas	High cuboidal	1	1	3
E-12	F	110	Moderate size	Flat	3	0	0
E-13	M	140	Small; tubes, solid areas	High cuboidal	1	1	3
E-14	F	200	Moderate size	Cuboidal	2	1	1
E-15	M	135	Moderate, small; solid areas	Cuboidal	1	0	2
E-16	M	130	Small; tubes, solid areas	High cuboidal	1	0	3
E-17	M	120	Small size; tubes	Cuboidal	1	1	2
E-18	M	145	Moderate, small; tubes, solid areas	High cuboidal	2	1	3

iodine and none in those fed on a diet high in calcium lactate and low in iodine, the conclusions are not absolutely clear. The data would rather indicate that the positive element in this series of experiments was the chlorine and not the calcium ion. Whether this action is specific for chlorine or may occur with other halogens is not absolutely proved in this study. Further investigation, including verification of this work in a larger series, a series in which another calcium ingredient is used, and other halogens employed, is to be done and reported on later.

SUMMARY

White rats fed on a diet low in iodine in a relatively nonendemic region failed to have thyroid hyperplasia.

Changes in the thyroid gland did not occur in rats fed on a diet poor in vitamins and leafy vegetables.

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13. McCarrison, R.: A Goiter Survey in Albino Rats, Brit. M. J. **2**:989 (May 31) 1930.

A 2 per cent solution of calcium chloride, combined with a diet low in iodine, produced a definite thyroid hyperplasia in a large percentage of the experimental animals.

Hyperplasia was not observed in experimental rats fed on a diet high in calcium lactate and low in iodine.

Definite changes in the thyroid gland, similar to those obtained by a diet high in calcium chloride and low in iodine, were found in rats fed on a diet high in sodium chloride and low in iodine. This suggests that chlorine (or the halogens as a group) may act as a positive factor in the production of thyroid hyperplasia.

EFFECT OF INSULIN AND DEXTROSE ON THE NORMAL AND ON THE OBSTRUCTED INTESTINE

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NEW ORLEANS

The intravenous administration of dextrose solution has become popular both as a preoperative and as a postoperative therapeutic measure. In addition to supplying the body with the necessary fluids in cases of dehydration, dextrose solution also supplies food that is readily utilized. A hypertonic solution of dextrose is an excellent diuretic, and therefore is of value in the prevention and treatment of cerebral edema. Dextrose solution is useful in the treatment of shock, and by virtue of its caloric value it tends to prevent and combat the development of acidosis. Largely owing to the work of Thalhimer,[1] the combination of dextrose and insulin in the treatment of nondiabetic acidosis became popular. The use of this combination was continued for a considerable period of time, but within recent years it is the tendency among most clinicians not to use insulin but to administer dextrose alone. Dextrose is usually employed in 5 or 10 per cent dilutions, unless a dehydrating or diuretic effect is desired. The use of the continuous dextrose infusion ("intravenous drip"), as suggested by Matas,[2] is popular and frequently life-saving.

Bulatoa and Carlson,[3] in 1924, showed that the intravenous injection of from 5 to 10 Gm. of dextrose in 50 per cent solution produced an inhibition of the movement of the stomach that lasted from 10 to 60 minutes. Equimolar solutions of sodium chloride and the same amounts of 50 per cent lactose solution had no effect on gastric activity. The injection of from 20 to 40 units of insulin produced a marked increase in gastric

1. Thalhimer, W.: Insulin Treatment of Postoperative (Nondiabetic) Acidosis, J. A. M. A. **81**:383 (Aug. 4) 1923.

2. Matas, Rudolph: Continued Intravenous Drip, Ann. Surg. **79**:643 (May) 1924.

3. Bulatoa, E., and Carlson, A. J.: Contributions to the Physiology of the Stomach: Influence of Experimental Changes in Blood Sugar Level on Gastric Hunger Contractions. Am. J. Physiol. **69**:107, 1924.

activity. These same observers found that the intravenous injection of 5, 10 or 20 Gm. of dextrose in a diabetic dog following complete pancreatectomy did not produce typical prolonged hunger contractions. Bulatoa and Carlson [?] believe that these changes following the administration of dextrose and insulin are due to a change in the energy metabolism of the gastric motor tissue as a result of the available glycogen being reduced. Stucky, Rose and Cowgill [4] determined the effect of dextrose and insulin on the stomach in the presence of vitamin B deficiency. Five of the seven animals with vitamin B deficiency showed evidence of decreased gastric motility. Of sixteen experiments, four (25 per cent) showed that the injection of insulin was followed by an increase in gastric motility. In twelve (75 per cent), insulin produced no significant change in the motility of the empty stomach. Stucky and his co-workers concluded from this investigation that the disturbances in gastric motility resulting from vitamin B deficiency are not the result of hypoglycemia, and that the hypoglycemia produced by the administration of insulin in vitamin B-deficient animals does not alter gastric motility. They believe that in the 25 per cent of the cases in which increased gastric motility followed the administration of insulin the action was due to the insulin itself and not to vitamin B, as insulin contains no vitamin B. There was no relationship between the level of the blood sugar and the gastric motility. Quigley, Johnson and Solomon [5] showed in man, by placing balloons in different parts of the stomach, that the response to insulin and dextrose was qualitatively the same in all parts of the stomach. They found that characteristically the injection of insulin produced prolonged gastric activity associated with a marked and sustained increase in gastric tone. The administration of dextrose into the stomach did not produce the characteristic inhibition of gastric activity, whereas the gastric response following the intraduodenal administration of dextrose corresponded to that which followed the intravenous administration. Templeton and Quigley [6] determined the effect of dextrose and insulin on a Heidenhain pouch of the stomach. In contrast to the normal stomach, the Heidenhain pouch showed inhibition of motility and decrease of tone. This in some few cases lasted for as long as 4 hours. In those instances in which concomitant tracings were

4. Stucky, C. J.; Rose, W. B., and Cowgill, G. R.: Studies in the Physiology of Vitamins: VI. Effect of Insulin on Gastric Motility in Vitamin B Deficiency, Am. J. Physiol. **87**:85, 1928.

5. Quigley, J. P.; Johnson, V., and Solomon, E. I.: Effect of Insulin on the Motility of the Gastro-Intestinal Tract: Action on the Stomach of Normal Fasting Man, Am. J. Physiol. **90**:89, 1929.

6. Templeton, R. D., and Quigley, J. P.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: II. Action on the Heidenhain Pouch, Am. J. Physiol. **91**:467, 1930.

made of the pouch and the normal stomach, inhibition in the pouch occurred simultaneously with increased motility of the stomach. The intravenous administration of dextrose to the fasting animal with a Heidenhain pouch produced no change in activity of the pouch, but concomitant tracings of the stomach proper showed the characteristic inhibition. Templeton and Quigley [6] believe that the reaction produced by dextrose and insulin in a Heidenhain pouch differs from that in the stomach proper because in the former the nerve fibers from the vagi have been divided and probably disturbances in the plexuses of Meissner and Auerbach have occurred. They also suggested that the fundic portion of the stomach from which the pouch was made differs qualitatively from the pyloric portion. Quigley and Templeton [7] determined the effect of insulin and dextrose on a pyloric pouch and on the stomach proper following double splanchnicotomy. They found that before splanchnicotomy subcutaneous and intravenous injection of insulin did not modify the motility or the tone of the pyloric pouch. Similar negative results were obtained following the intravenous injection of dextrose, irrespective of whether the dextrose followed or preceded the insulin or was given alone. After double splanchnicotomy, it was found that there was a characteristic increase in gastric motility as described by Carlson. This increase was augmented by the subcutaneous injection of 20 units of insulin. The intravenous administration of dextrose produced a temporary decrease in gastric motility, whereas the administration of dextrose without an antecedent injection of insulin produced complete inhibition of gastric activity. The increased gastric activity was apparently slightly greater in the splanchnicotomized animals than in the normal animals. These same investigators [8] determined the reaction of the stomach to dextrose and insulin after vagotomy. All the animals showed the type of hunger contractions following vagotomy described by Carlson. As a rule, the injection of insulin, in contrast to the normal, produced an inhibition in gastric motility in the vagotomized animal, the inhibition lasting several hours. Quigley and Templeton [8] concluded from this that insulin apparently acts centrally, the impulses being carried over the vagi, and that following vagotomy impulses cannot be carried to the stomach. They agreed with Bulatoa and Carlson [3] that the gastric response to dextrose and insulin is not due to the dextrose and insulin per se, but is due to the changes in blood sugar and to the modified cell metabolism which are produced by the insulin and the

7. Quigley, J. P., and Templeton, R. D.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: III. A. Action on the Pyloric Pouch. B. Action on the Stomach Following Double Splanchnicotomy, Am. J. Physiol. **91**:475, 1930.

8. Quigley, J. P., and Templeton, R. D.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: IV. Action on the Stomach Following Double Vagotomy, Am. J. Physiol. **91**:482 (Jan.) 1930.

dextrose. The inhibiting effect that is exerted by the intravenous injection of dextrose on the stomach occurs probably through the vagi, for it is absent in the Heidenhain pouch and in the stomach after vagotomy. The assumption that the stimulating influences reaching the stomach after the injection of insulin pass by way of the vagi is substantiated by the investigations of Wilder and Schlutz.[9] They found that the administration of atropine to an animal with gastric hyperactivity produced by insulin caused marked inhibition (often complete cessation) of gastric motility and loss in tone. This was associated with a lowering of the blood sugar. They believe that the stimulating effect of insulin on the stomach is due to hyperirritability of the vagi. Quigley and Solomon [10] in determining the effect of insulin and dextrose on the human stomach found that following the subcutaneous administration of insulin increased duodenal and gastric activity occurred. The increase in duodenal activity, which usually occurred about 15 minutes before the gastric activity became marked, consisted largely of an increase in the frequency of the contraction with little change in the tone. At the time that the gastric movements began, they became more frequent than those in the duodenum. The administration of atropine, and also of a dextrose solution by mouth, completely stopped the movements in the duodenum and stomach. Quigley and Solomon [10] also found, by introducing balloons through an appendectomy wound in animals, that following the administration of insulin there was an increase in colonic movement. The stimulation occurred more uniformly in the colon than in the stomach. The administration of dextrose caused complete cessation of colonic movement, which, however, was less complete than that seen in the stomach. Quigley and Barnes,[11] determining the effect of pituitary extract and insulin on the stomach, found that pituitary preparations invariably produced diminution in gastric activity. Associated with this was a slight rise in blood sugar, which, however, was not sufficient to account for the diminished gastric activity. The administration of pituitary preparations to insulinized animals produced a similar inhibition in the motility of the stomach. Relatively recently, Quigley and Hallaran [12] concluded from their investigations that the spontaneous

9. Wilder, R. L., and Schlutz, F. W.: Action of Atropine and Adrenaline on Gastric Tonus and Hypermotility Induced by Insulin Hypoglycemia, Am. J. Physiol. **96**:54, 1931.

10. Quigley, J. P., and Solomon, E. I.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: V. A. Action on the Human Duodenum. B. Action on the Colon of Dogs, Am. J. Physiol. **91**:488 (Jan.) 1930.

11. Quigley, J. P., and Barnes, B. O.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: VI. Antagonistic Action of Posterior Pituitary Lobe Preparations, Am. J. Physiol. **95**:7, 1930.

12. Quigley, J. P., and Hallaran, W. R.: The Independence of Spontaneous Gastro-Intestinal Motility and Blood Sugar Levels, Am. J. Physiol. **100**:102, 1932.

motility of the stomach and intestine is unaffected by the intravenous injection of dextrose solution, whereas the increased activity produced by insulin is inhibited. They feel that the changes occurring in the motility of the stomach and intestine following the intravenous injection of dextrose solutions are inconsequential.

Because of the alterations in motility of the normal stomach and duodenum of man and animals and the normal intestine of animals produced by the administration of dextrose and insulin, and because dextrose solutions are so universally employed clinically, especially in the "poor risk" patient (including those with ileus), it was considered advisable to determine the effect which these substances exert on the normal and on the obstructed small intestine.
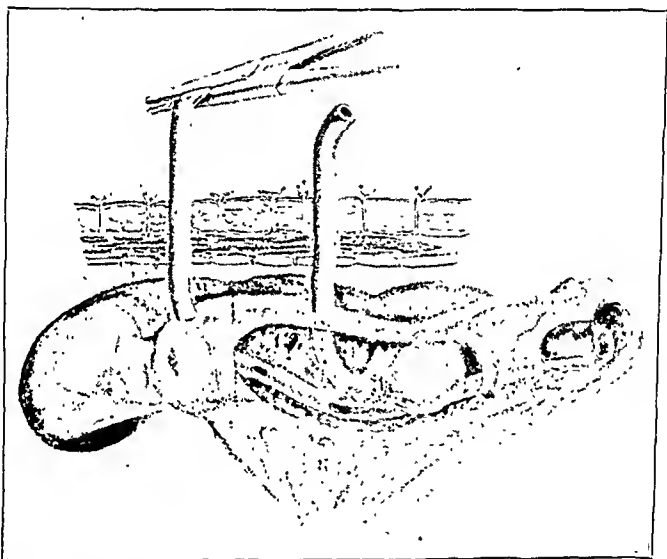
Fig. 1.—Drawing illustrating the relative arrangement of the enterostomy tube and the tube carrying the balloon used to record intestinal movement. As illustrated, the terminal ileum has been divided and the two ends inverted. A fenestrated enterostomy tube is introduced into the distal end of the proximal portion of the ileum and allowed to extend proximally in the intestine for approximately 20 cm. About 5 cm. proximal to this a rubber tube carrying a balloon is introduced proximally into the intestine but not extending beyond the end of the enterostomy tube. As long as the enterostomy tube is open, an obstruction is not present. However, an obstruction may be produced by clamping, as illustrated in the diagram, or by tying the tube.

Ninety-two observations were made on thirty dogs, twenty-two on the normal animal, thirteen on animals with 24 hour obstruction, twenty-two on animals with 48 hour obstruction, twenty-five on animals with 72 hour obstruction, and ten on animals with 96 hour obstruction. The effect on intestinal activity of insulin alone was determined seventeen

times; of dextrose alone, sixteen times; of dextrose and insulin combined, ten times; of insulin preceded by dextrose, ten times, and of dextrose preceded by insulin, thirty-nine times. All observations were made on unanesthetized animals. This and repeated observations on the same animal were made possible by employing the following technic.[13]

TECHNIC

Under aseptic precautions, the terminal ileum was divided and each end inverted by a purse string suture. About 5 cm. proximal to the inverted end of the proximal portion, a fenestrated tube was introduced through an enterostomy opening and allowed to extend proximally in the lumen of the bowel for about 21 cm. About 5 cm. proximal to this, a second tube carrying a balloon was introduced through another enterostomy opening, the end carrying the balloon being directed proximally, but so placed that the fenestrated enterostomy tube extended beyond the balloon (fig. 1). Both tubes were brought out through the omentum, and the abdominal wall was closed in layers. The animal was allowed to recover completely, and after 24 hours the tube carrying the balloon was connected with a
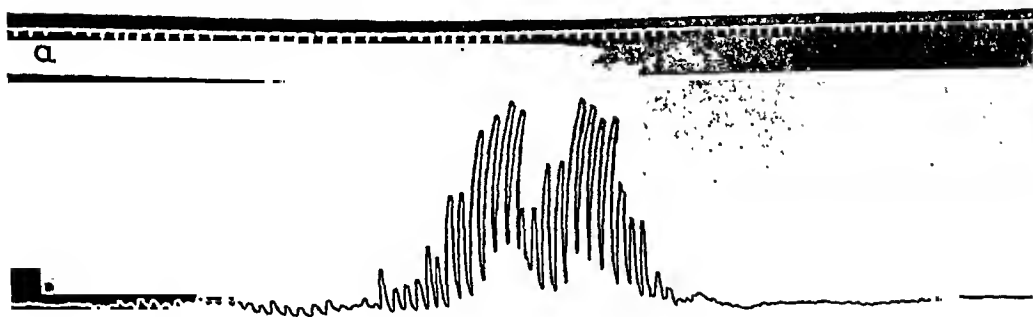
Fig. 2.—Kymographic tracing showing the effect of insulin on the activity of the normal intestine.   Time is indicated by a (in all the figures the time interval between the small vertical bars is one-tenth minute, or six seconds).   Tone and movement of the ileum are indicated by b.   The tracing was taken 40 minutes after the administration of insulin. There was not only an increase in tone, but also a marked increase in amplitude of intestinal movement.

Marey tambour, and kymographic tracings were obtained. Concomitant respiratory tracings were made. Observations were made on the normal unanesthetized animal, following which the enterostomy tube was clamped, producing a mechanical obstruction. Observations were made daily as long as the animal survived. Blood sugar determinations were made before the beginning of the experiment and at intervals subsequently, an attempt being made to obtain a specimen at the height of the intestinal activity. Blood sugar determinations were made by Folin-Wu technic.

The doses of insulin and dextrose varied in different experiments, but in each instance the dextrose was given intravenously as a 10 per cent solution; the

13. Gage, I. M.; Ochsner, Alton, and Cutting, R. A.: Effect of Insulin and Glucose on Normal and Obstructed Intestine, Proc. Soc. Exper. Biol. & Med. **29:** 264, 1931.

amounts were usually between 6 and 10 Gm., with an average of 7.5 Gm. Large doses of insulin were used and were given intravenously; the dose varied between 20 and 40 units. In only four instances were there hypoglycemic manifestations. It was found that the average period of time before changes in the intestinal activity occurred after the intravenous injection of insulin was 30 minutes, whereas the changes that followed the intravenous administration of dextrose occurred usually within a few minutes.

The results are based on an analysis of the kymographic tracings.

EFFECT OF INSULIN ALONE ON THE NORMAL AND THE OBSTRUCTED INTESTINE

Normal Intestine.—One observation was made on the normal intestine 30 minutes after the intravenous administration of 40 units of insulin. There was a decrease in blood sugar from 159 to 151 mg. per hundred cubic centimeters (5 per cent decrease). The intestinal tone and amplitude were increased 30 and 16 mm., respectively (fig. 2). The increased activity lasted 6 minutes.

Fig. 3.—Kymographic tracing showing the effect of insulin on an intestine that had been obstructed for 24 hours. Time is indicated by *a*, tone and movement of the ileum by *b*, and respiration by *c*. The tracing was taken 34 minutes after the administration of insulin. The increase in tone was not especially marked, but the increase in intestinal movement was very definite.

Twenty-Four Hour Obstruction.—One observation was made. After the administration of 20 units of insulin, there was a decrease in blood sugar from 107 to 61 mg. per hundred cubic centimeters (43 per cent decrease). There was an increase in intestinal tone and amplitude of 4 and 18 mm., respectively (fig. 3). The duration of this increased activity was 2 minutes.

Forty-Eight Hour Obstruction.—Five observations were made. In each instance, 40 units of insulin was used, and in every case a decrease in blood sugar occurred, from a normal average of 119 mg. to 74 mg. per hundred cubic centimeters (37 per cent decrease). The observations were made between 30 and 40 minutes after the administration of insulin with one exception in which the interval was 58 minutes. In only two instances was there an increase in intestinal activity, the average increase in tone and amplitude being 10 and 1.5 mm., respectively. The average length of time of increased intestinal activity was 12 minutes. In the instances in which increased activity occurred, the blood sugar was decreased from an average normal of 159 mg. to 103 mg. per hundred cubic centimeters (29 per cent decrease), whereas in those instances in which no change occurred,

the blood sugar decreased from an average normal of 93 mg. to 55 mg. (42 per cent decrease). In three observations (60 per cent), there was no change in the activity of the intestine.

Seventy-Two Hour Obstruction.—Seven observations were made. Forty units of insulin was given in six instances and 10 units in one. In each instance there was a decrease in blood sugar from an average blood sugar value of 105 mg. to 72 mg. per hundred cubic centimeters (22 per cent decrease). The observations

TABLE 1.—*Effect of Insulin Alone on the Activity of the Intestine*

Condition of Intestine; Number of Observations	Intestine			Blood	
	Increase	No Change	Decrease	Increase	Decrease
Normal; 1..............	100% T 30; A 16; T' 6 B 159; B' 151; —5%	....	....	....	100% B 159; B' 151; —5%
24 hr. obstruction; 1....	100% T 4; A 18; T' 2 B 107; B' 61; —43%	....	....	....	100% B 107; B' 61; —40%
48 hr. obstruction; 5....	40% T 10; A 1.5; T' 12 B 159; B' 103; —29%	60% B 93; B' 55; —42%	....	....	100% B 110; B' 74; —37%
72 hr. obstruction; 7....	43% T 4; A 25; T' 6 B 123; B' 77; —37%	43% B 82; B' 57; —30%	14% T 10; A 0; T' 37 B 112; B' 62; —44%	....	100% B 105; B' 72; —22%
96 hr. obstruction; 3....	66% T 7; A 3.5; T' 5.5 B 113; B' 49; —56%	33% B 115; B' 93; —19%	....	....	100% B 114; B' 64; —44%

The number of dogs in which there was an increase, no change or a decrease in activity of the intestine is expressed in percentage. The average increases in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (E') is expressed in minutes. The average blood sugar values before (B) and after (B') the administration of insulin are given in milligrams, with the percentage of loss.

were made at varying periods of time after the administration of insulin. All with the exception of one (which was made after 11 minutes) were made between 30 and 40 minutes after the administration of insulin. In three instances there was an increase in intestinal activity, the average increase in tone and amplitude being 4 and 25 mm., respectively. The average duration of the increased activity was 6 minutes. In three instances there was no change, and in one there was an actual decrease in activity of the intestine. In the one instance in which a decrease in activity occurred, there was a fall in tone of 10 mm., which persisted for 37 minutes. The average blood sugar values before the administration of insulin in the

instances in which there was an increase, no change or a decrease in intestinal activity were 123, 83 and 112 mg. per hundred cubic centimeters, respectively. The average blood sugar values after the administration of insulin for the same groups were 77, 57 and 62 mg. per hundred cubic centimeters, respectively.

Ninety-Six Hour Obstruction.—Three observations were made. Forty units of insulin was administered intravenously in each instance. Observations were made 25, 37 and 58 minutes, respectively, after the administration of insulin. In one instance, the blood sugar determinations for technical reasons were unreliable and were, therefore, discarded. In the other two there was a definite decrease in blood sugar from a normal average of 114 mg. to 64 mg. per hundred cubic centimeters. An increase in intestinal activity occurred in two instances, an average increase in tone and amplitude of 7 and 3.5 mm., respectively. The average duration of the increased activity was 5.5 minutes. In one of the three animals, no change in intestinal activity occurred.

EFFECT OF DEXTROSE ALONE ON THE NORMAL AND THE OBSTRUCTED INTESTINE

Normal Intestine.—Seven observations were made. In each instance, 75 cc. of 10 per cent dextrose solution was administered intravenously. In two animals, the

Fig. 4.—Kymographic tracing showing the inhibiting effect of dextrose on a normal intestine that had been made hyperactive by means of splanchnic analgesia. Time is indicated by *a*, tone and movement of the ileum by *b*, and respiration by *c*. At the extreme left, following splanchnic analgesia, there occurred a marked increase in intestinal activity as evidenced by the increase in tone and amplitude of intestinal movement. At about the midportion of the kymographic tracing an infusion of 10 per cent dextrose was started and continued approximately 5.5 minutes, at which time 75 cc. had been administered. Within 1 minute after the completion of the infusion, as shown in the right hand portion of the tracing, there was a rapid fall in intestinal tone with almost complete absence of movement. The tone assumed a lower level than that before the splanchnic analgesia.

dextrose was administered without any previous procedures having been used. In five, hyperperistalsis had been produced by means of either intravenous injection of hypertonic salt solutions or splanchnic block (fig. 4). Following the administration of dextrose there was in each instance a definite decrease in intestinal activity, the average decreases in tone and amplitude being 27.2 and 10.6 mm., respectively (fig. 4). The average duration of this inhibition was over 13 minutes.

In five instances in which blood sugar determinations were made at such times that they could be correlated with the intestinal movement, there occurred a marked increase from an average normal of 148 mg. to 298 mg. per hundred cubic centi-

meters of blood (101 per cent increase). The percentage increases in blood sugar varied from 37 to 171 per cent.

Twenty-Four Hour Obstruction.—Three observations were made. In each instance, peristalsis had been induced by intravenous injection of hypertonic salt solutions; the dextrose was administered at the height of the intestinal activity (fig. 5). The interval of time between the administration of dextrose and the first effect on the intestine varied from 2 to 9 minutes. Seventy-five cubic centimeters of 10 per cent solution was employed in each instance. The blood sugar was increased in two of the three observations from a normal average of 119 mg. to 202 mg. per hundred cubic centimeters of blood. The intestinal movement was decreased in each instance, there being average decreases in tone and amplitude of 38 and 5 mm., respectively. This inhibition persisted for an average of 19 minutes.

Forty-Eight Hour Obstruction.—Four observations were made. In one instance, dextrose was given alone without any previous medication; in the remaining three, hypertonic chloride solutions had been employed to stimulate the intestine. Seventy-five cubic centimeters of 10 per cent dextrose solution was used in each instance.

Fig. 5.—Kymographic tracing showing the inhibiting effect of dextrose solution on an intestine which had been obstructed for 24 hours and which had been made hyperactive by an intravenous administration of hypertonic salt solution. Time, tone and movement of the ileum, and respiration are represented by *a, b* and *c*. As shown on the left of the tracing, there was an increase principally in intestinal tone, but also some increase in intestinal movement, following the intravenous administration of 10 cc. of 20 per cent salt solution. Just to the right of the mid-portion of the tracing an infusion of 10 per cent dextrose was begun. Within 2 minutes after the start of the infusion there was a cessation of all intestinal movement with rapid loss in intestinal tone.

The blood sugar was increased in each instance from a normal average of 121 mg. to 282 mg. per hundred cubic centimeters of blood (133 per cent increase). The individual percentage increases in blood sugar varied from 128 to 224. In every instance, there was an inhibition of the intestinal activity, there being average decreases in tone and amplitude of 15 and 5 mm., respectively. The average duration of this inhibition was more than 6 minutes.

Seventy-Two Hour Obstruction.—Two observations were made. In each instance, the intestine had been activated by a previous administration of hypertonic salt solution. Seventy-five cubic centimeters of 10 per cent dextrose was injected intravenously. The average interval of time between the infusion and the effect produced on the intestine was 15 minutes. There occurred a marked increase in

blood sugar in each instance from an average normal of 97 mg. to 231 mg. per hundred cubic centimeters of blood (141 per cent average increase). There was a decrease in intestinal tone and amplitude in both instances. The activity of the intestine was definitely decreased in each instance, the average decreases in tone and amplitude of movement being 10 and 10 mm., respectively. The average duration of the inhibition was 10 minutes.

EFFECT OF INSULIN AND DEXTROSE COMBINED ON THE NORMAL AND THE OBSTRUCTED INTESTINE

Normal Intestine.—Three observations were made. In two instances, 75 cc., and in one, 60 cc. of a 10 per cent dextrose solution was administered. In two

TABLE 2.—*Effect of Dextrose Alone on the Activity of the Intestine*

Condition of Intestine; Number of Observations	Intestine			Blood	
	Increase	No Change	Decrease	Increase	Decrease
Normal; 7..............	....	....	100% T 27.2; A 10.6; T′ 13+ B 148; B′ 298; +101%	100% B 148; B′ 298; +101%	....
24 hr. obstruction; 3....	....	....	100% T 38; A 5; T′ 19 B 163; B′ 184; +12%	66.6% B 119; B′ 202; +69%	33.3% B 250; B′ 149; —40% B 163; B′ 184; +12%
48 hr. obstruction; 4....	....	....	100% T 15; A 5; T′ 6 B 121; B′ 282; +133%	100% B 121; B′ 282; +133%	....
72 hr. obstruction; 2....	....	....	100% T 10; A 10; T′ 10 B 97; B′ 231; +141%	100% B 97; B′ 231; +141%	....

The number of dogs in which there was an increase, no change or a decrease is expressed in percentage. The average increases in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (T′) is expressed in minutes. The average blood sugar values before (B) and after (B′) the administration of dextrose are given in milligrams, with the percentage of gain or loss.

instances, 40 units, and in one, 20 units, of insulin was given. Blood sugar determinations were made 38 minutes after the intravenous infusion. In two instances, the blood sugar was increased from a normal average of 81 mg. to 102 mg. per hundred cubic centimeters of blood (26 per cent increase) whereas in one the blood sugar was decreased from a normal value of 106 mg. to 73 mg. per hundred cubic centimeters. In only one instance was there a slight increase in intestinal activity as evidenced by an increase in amplitude of movement of 1 mm., which persisted. In two instances, no change occurred in the intestinal activity.

Twenty-Four Hour Obstruction.—Three observations were made. In each instance, 75 cc. of 10 per cent dextrose solution and 40 units of insulin were used.

The time elapsing between the administration of the solution and the appearance
of intestinal activity varied from 54 to 57 minutes. The blood sugar was decreased
in each instance from an average normal value of 136 mg. to 75 mg. per hundred
cubic centimeters of blood (159 per cent decrease). There was an increase in
intestinal tone of 5 mm. in one instance, a decrease in tone of 9 mm. in another,
and in a third the intestinal activity was not changed. The normal blood sugar
value, i. e., before the administration of dextrose and insulin, was higher (167 mg.)
in the animal in which increased activity of the intestine occurred than that (106
mg.) in the animal in which there resulted no change in activity.

TABLE 3.—*Effect of Dextrose and Insulin Combined on Activity of the Intestine*

Condition of Intestine; Number of Observations	Intestine			Blood Sugar	
	Increase	No Change	Decrease	Increase	Decrease
Normal; 3.............	33.3% T 0; A 1; T' cont. B 97; B' 107; +15%	66.6% B 87; B' 85; —2%	....	66.6% B 81; B' 102; +26%	33% B 106; B' 73; —31%
				B 89; B' 03; +18%	
24 hr. obstruction; 3....	33.3% T 5; A 0 B 167; B' 77; —31%	33.3% B 106; B' 73; —31%	33.3% T 9; A 0	....	100% B 138; B' 75; —59%
48 hr. obstruction; 3....	33.3% T 0; A 5; T' 6 B 100; B' 71; —29%	66.6% B 87; B' 57; —34%	....	....	100% B 94; B' 64; —32%
72 hr. obstruction; 1....	100% T 27; A 12; T' 16 B 97; B' 79; —18%	....	....	....	100% B 97; B' 79; —18%

The number of dogs in which there was an increase, no change or a decrease in activity of
the intestine is expressed in percentage. The average increases in tone (T) and amplitude (A)
of intestinal movement are expressed in millimeters. Time (T') is expressed in minutes. The
average blood sugar values before (B) and after (B') the combined administration of dextrose
and insulin are given in milligrams with the percentage of gain or loss.

Forty-Eight Hour Obstruction.—Three observations were made. In two
instances, 75 cc., and in one, 80 cc. of 10 per cent dextrose solution was introduced
intravenously. In each instance, the amount of insulin combined with the dextrose
was 40 units. Intestinal activity became evident between 30 and 35 minutes after
the intravenous administration of the dextrose and insulin. The blood sugar
decreased in each instance from an average normal value of 94 mg. to 64 mg. per
hundred cubic centimeters of blood (32 per cent decrease). In two instances, no
change in intestinal activity occurred. In one, however, there was an increase in
amplitude of movement of 5 mm. without a concomitant rise in tone, which per-
sisted approximately 6 minutes. The preliminary blood sugar value in the
animal in which increased intestinal activity followed the injection of dextrose and

insulin was 100 mg. per hundred cubic centimeters as compared with the average blood sugar value of 87 mg. in the two animals in which no intestinal response occurred.

Seventy-Two Hour Obstruction.—One observation was made. Seventy-five cubic centimeters of 10 per cent dextrose solution and 10 units of insulin were given intravenously. The stimulating effect on the intestine was noted 18 minutes after the administration. The blood sugar was decreased from 97 to 79 mg. per hundred cubic centimeters of blood. The effect on the intestine was marked, in that the intestinal tone and amplitude were increased 27 and 12 mm., respectively, which effect persisted approximately 16 minutes (fig. 6).

Fig. 6.—Kymographic tracing showing the effect of dextrose solution and insulin combined on the 72 hour-obstructed intestine. There are three definite periods of increased intestinal activity, each consisting of an increase in tone and intestinal movement. These periodic increases in intestinal activity correspond to the cramplike pain experienced by human beings.

Fig. 7.—Kymographic tracing showing the effect on the normal intestine of the administration of insulin which had been preceded by an intravenous infusion of dextrose. Time, tone and movement of ileum, and respiration are represented by *a, b* and *c*. As illustrated in the left part of the tracing, the infusion of dextrose caused a cessation of intestinal movement. Nine minutes after completion of the dextrose infusion, insulin was administered, and 7 minutes later, as shown in the right portion of the tracing, there was a definite increase in intestinal tone and also in intestinal movement.

EFFECT OF INSULIN PRECEDED BY DEXTROSE ON THE NORMAL AND THE OBSTRUCTED INTESTINE

Normal Intestine.—Two observations were made. In each instance, the animal had received not only dextrose prior to the administration of the insulin, but a combination of dextrose and insulin. In one, subsequent to the initial infusion with dextrose and insulin, the animal had received two injections each of 75 cc. of 10 per cent dextrose solution before the insulin was given. Increased intestinal

activity occurred 7 minutes and 25 minutes, respectively, after the injection of 40 units of insulin (fig. 7). In each instance, there was a decrease in blood sugar from an average normal value of 193 mg. to 139 mg. per hundred cubic centimeters of blood (25 per cent decrease). In one instance, there was no effect on the intestinal activity; in the other, however, 7 minutes after the intravenous administration of insulin, there was a definite increase in activity as evidenced by an increase in tone and amplitude of 39 and 3 mm., respectively, which persisted 6 minutes.

TABLE 4.—*Effect of Insulin Preceded by Dextrose on the Activity of the Intestine*

Condition of Intestine; Number of Observations	Intestine			Blood Sugar	
	Increase	No Change	Decrease	Increase	Decrease
Normal; 2..............	50% T 39; A 3; T′ 6 B 288; B′ 210; —27%	50% B 98; B′ 69; —29%	....	....	100% B 193; B′ 139; —25%
24 hr. obstruction; 1....	100% T 20; A 2; T′ 2	....	....	....	....
48 hr. obstruction; 2....	100% T 13; A 4; T′ 12+++ B 207; B′ 105; —49%	....	....	....	100% B 207; B′ 105; —49%
72 hr. obstruction; 3....	66% T 2.5; A 3.5; T′ 8 B 204; B′ 48; —54%	33% B 182; B′ 43; —76%	....	....	100% B 130; B′ 46; —64%
96 hr. obstruction; 2....	50% T 3; A 2; T′ 8 B 214; B′ 96; —55%	50% B 205; B′ 79; —61%	....	....	100% B 209; B′ 87; —58%

The number of dogs in which there was an increase, no change or a decrease in activity of the intestine is expressed in percentage. The average increase in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (T′) is expressed in minutes. The average blood sugar values before (B) and after (B′) the administration of insulin preceded by dextrose are given in milligrams, with the percentage of loss or gain.

Twenty-Four Hour Obstruction.—One observation was made. Twenty units of insulin was given 9 minutes after an intravenous injection of 75 cc. of 10 per cent dextrose solution. An increase in intestinal activity occurred 10 minutes after the administration of insulin. No blood sugar determinations were made. There was an increase in intestinal activity. The intestinal tone and amplitude were increased 20 and 2 mm., respectively, which activity lasted 2 minutes.

Forty-Eight Hour Obstruction.—Two observations were made. In one instance in which 50 cc. of 10 per cent dextrose solution was given 6 minutes before 40

units of insulin, increased intestinal activity was noted 28 minutes after the administration of insulin. In the other in which an injection of 50 cc. of 10 per cent dextrose preceded the administration of insulin by 24 minutes, activity occurred 6 minutes after the injection of insulin. In each instance, there was a decrease in blood sugar from a normal value of 207 mg. to 105 mg. per hundred cubic centimeters (49 per cent decrease). The intestine was definitely stimulated in each case, there being average rises in tone and amplitude of 13 and 4 mm., respectively, which effect persisted in one for 8 minutes until another infusion of dextrose was made, and in the other for longer than 20 minutes (fig. 8).

Seventy-Two Hour Obstruction.—Three observations were made. In each instance prior to the administration of dextrose that preceded the administration of insulin, a previous administration of insulin had been given. The intestinal effect occurred, on an average, 12 minutes after the intravenous administration of 40 units of insulin in two cases and 20 units in one case. In each instance, there was a decrease in blood sugar from a normal average value of 130 mg. to 46 mg. per hundred cubic centimeters of blood (64 per cent decrease). In one instance there was no change in intestinal activity. In two there occurred a stimulation of
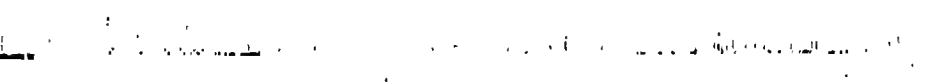
Fig. 8.—Kymographic tracing showing the effect of an administration of insulin preceded by an intravenous infusion of dextrose on an intestine that had been obstructed for 48 hours. Time, tone and movement of the ileum, and respiration are represented by *a, b* and *c.* As seen in the left portion of the tracing, the intestine was inactive. About the midportion of the tracing, 26 minutes after the administration of insulin there occurred periodic increases in intestinal activity, consisting primarily in increases in amplitude of intestinal movement.

the intestine, as evidenced by average rises in tone and amplitude of 2.5 and 3.5 mm., respectively. The average duration of the increased activity was 8 minutes.

Ninety-Six Hour Obstruction.—Two observations were made. In each instance, an injection of insulin had been made before the infusion of dextrose preceding the second injection of insulin. In both instances, 40 units of insulin was used. The observations were made 47 and 52 minutes, respectively, after the intravenous injection of the insulin. In each instance, there was a decrease in blood sugar from a normal average value of 209 mg. to 87 mg. per hundred cubic centimeters of blood (58 per cent decrease). In one instance, there was no change in the intestinal activity; in the other, however, there were increases in tone and amplitude of 3 and 2 mm., respectively, which persisted over 8 minutes. The preliminary blood sugar values in the animal in which stimulation of the intestine occurred was 214 mg. as compared with 205 mg. per hundred cubic centimeters in the animal in which no response occurred.

EFFECT OF DEXTROSE PRECEDED BY INSULIN ON THE NORMAL AND THE OBSTRUCTED INTESTINE

Normal Intestine.—Nine observations were made. In seven of these, the blood sugar determinations were complete, so that a correlation between the intestinal activity and the blood sugar could be made. In four not only a previous injection of insulin, but also a previous infusion with dextrose had been made. The interval between the injection of insulin and the appearance of effect on the intestine varied

TABLE 5.—*Effect of Dextrose Preceded by Insulin on the Activity of the Intestine*

Condition of Intestine; Number of Observations	Intestine			Blood Sugar	
	Increase	No Change	Decrease	Increase	Decrease
Normal; 9..............	71% T 46.3; A 14.4; T′ 8.3 B 130; B′ 270; +107%	14.8% B 69; B′ 142; +105%	14.8% T 5; A 4; T′ 4.5 B 125; B′ 288; +130%	100% B 119; B′ 263; +142%	....
24 hr. obstruction; 5....	80% T 50.8; A 7.5; T′ 3 B 128; B′ 263; +105%	20% B 83; B′ 174; +109%	....	100% B 107; B′ 242; +126%	....
48 hr. obstruction; 8....	62% T 18; A 11.6; T′ 10 B 71; B′ 249; +264%	25% B 65; B′ 255; +289%	12% T −4; A 1.5; B 121; B′ 200; +64%	100% B 74; B′ 220; +196%	....
72 hr. obstruction; 12...	83% T 22.2; A 7.8; T′ 8.2++ B 88; B′ 207; +135%	8.3% B 40; B′ 182; +355%	8.3% T 1; A 2; T′ 24 B 48; B′ 102; +112%	83.3% B 75; B′ 218; +178%	16.6% B 104; B′ 96; −17%
				B 80; B′ 179; +124%	
96 hr. obstruction; 5....	60% T 7; A 2; T′ 4.5 B 55; B′ 152; +177%	40% B 105; B′ 209; +99%	....	100% B 74; B′ 174; +139%	....

The number of dogs in which there was an increase, no change or a decrease in activity of the intestine is expressed in percentage. The average increases in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (T′) is given in minutes. The average blood sugar values before (B) and after (B′) the administration of insulin preceded by dextrose are given in milligrams, with the percentage of gain or less.

between 31 and 125 minutes; in the majority it was between 40 and 80 minutes. Within a very short time after the infusion with dextrose (from immediate response up to 7 minutes), the intestinal effect occurred (fig. 9). In only one instance was the time as long as 25 minutes. In all but two cases, 75 cc. of 10 per cent dextrose solution was used, and in all but one instance, 40 units of insulin was employed. In each instance there was an increase in the blood sugar from a normal average value of 119 mg. to 263 mg. per hundred cubic centimeters of blood (142 per cent increase). The average percentage increases in blood sugar varied from 43 to 288.

In seven (71 per cent) of the nine observations, there was a definite increase in intestinal activity as evidenced by average increases in tone and amplitude of 46.3 and 14.4 mm., respectively. The increases in tone varied from 5 to 85 mm., and the increases in amplitude varied from 3 to 25 mm. The average duration of the increased intestinal activity was 8 minutes. In one instance there was no change, and in another instance there was a decrease in the intestinal activity, there being decreases in tone and amplitude in the latter of 5 and 4 mm., respectively.

Twenty-Four Hour Obstruction.—Five observations were made. In each instance, the time that elapsed between the administration of insulin and the time that observations were made was relatively long, varying from 50 to 83 minutes. In three of the five instances, the original insulin (40 units) was combined with 75 cc. of 10 per cent dextrose solution. In each instance, there was an increase in blood sugar from a normal average value of 107 mg. to 242 mg. per hundred cubic centimeters of blood (126 per cent increase). The percentage increases in blood sugar varied from 108 to 226. There was an increase in intestinal activity in four,

Fig. 9.—Kymographic tracing showing the effect of insulin on a normal intestine. Time, tone and movement of the ileum, and respiration are represented by *a, b* and *c*. As shown in the extreme left portion of the tracing, immediately following the completion of the infusion of 75 cc. of 10 per cent dextrose solution there was a marked increase in intestinal activity consisting of, an increase in both tone and amplitude of movement.

and no effect was noted in one. The increases in intestinal tone varied from 20 to 88 mm., with an average of 50 mm. The increases in amplitude varied from 2 to 20 mm. and averaged 7.5 mm. The average duration of the increased activity was 3 minutes. In the four instances in which an increase in intestinal activity occurred, the average blood sugar value before the administration of the dextrose solution was 128 mg. per hundred cubic centimeters, whereas the preliminary blood sugar in the one instance in which there was no change in intestinal activity was 83 mg. per hundred cubic centimeters of blood.

Forty-Eight Hour Obstruction.—Eight observations were made. The time that elapsed following the administration of the original insulin varied from 55 to 115 minutes. The time elapsing after the administration of the dextrose solution varied from 2 to 75 minutes. In the majority of instances, however, it was less than 25

minutes. In several instances, a number of infusions, as many as three, of 10 per cent dextrose had been given before the present observations were made. In four instances, 50 cc., and in four instances, 75 cc. of 10 per cent dextrose solution was given after the insulin. The blood sugar was increased in each instance from a normal average of 74 mg. to 220 mg. per hundred cubic centimeters of blood (196 per cent increase). There was an increase in intestinal activity in five observations, and no change in two and a decrease in one. In those instances in which the intestinal activity was increased, the increases in intestinal tone varied from 10 to 28 mm., with an average of 11.6 mm. This increased activity persisted for an average of 10 minutes. In the one instance in which a decrease in activity occurred, there was a decrease in tone of 4 mm., and a decrease in amplitude of 1.5 mm.

Seventy-Two Hour Obstruction.—Twelve observations were made. In all of these, except one, blood sugar determinations were made. In many of the instances, repeated administrations of dextrose were made before the injection of insulin; in seven, two administrations of dextrose were made before the one that followed the injection of insulin. The length of time between the original administration of
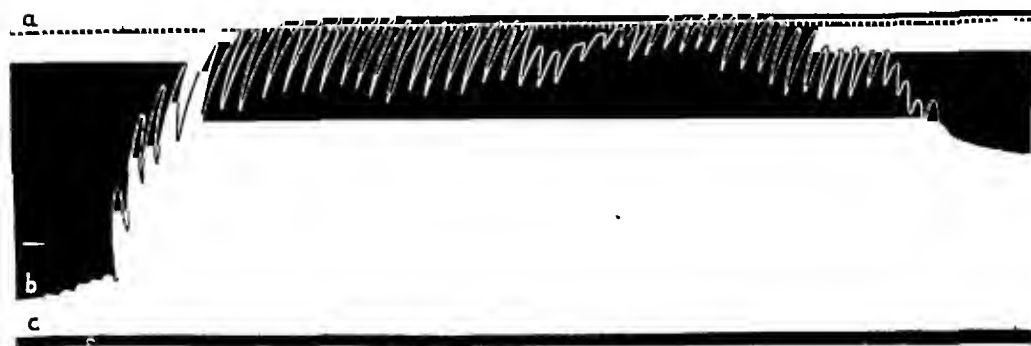
Fig. 10.—Kymographic tracing showing the effect of an intravenous administration of dextrose which had been preceded by an administration of insulin on an intestine that had been obstructed for 72 hours. Time, tone and movement of the ileum, and respiration are represented by *a, b* and *c*. As shown in the extreme left portion of the tracing there was no intestinal movement. After the administration of approximately 15 cc. of 10 per cent dextrose solution there was a marked increase in intestinal tone, with an increase in amplitude of intestinal movement. This persisted, following which there was a cessation of movement. The tone, however, remained elevated.

insulin and the present observations varied from 41 to 362 minutes. The length of time from the infusion of dextrose to the observations herein reported varied from 1 to 58 minutes; in the majority of instances, however, the time was between 20 and 30 minutes. With one exception (in which only 10 units of insulin was used), the original amount of insulin employed was 40 units. With but three exceptions (in which 50 cc. was used), 75 cc. of 10 per cent dextrose was employed. In ten (83.3 per cent) of the twelve observations, the blood sugar was increased from an average normal of 75 mg. to 218 mg. per hundred cubic centimeters of blood (178 per cent increase). In two instances (16.6 per cent), a decrease in blood sugar occurred from a normal average of 104 mg. to 86 mg. (17 per cent

decrease). In ten (83.3 per cent) of the twelve instances, there resulted an increase in intestinal activity; the increases in tone varying from 3 to 60 mm., with an average of 22.2 mm.; the increases in amplitude varying from 2 to 25 mm., the average being 7.8 mm. (fig. 10). The average duration of this increased activity was over 8.2 minutes. In one instance there resulted no change in intestinal activity, and in one there were decreases in tone and amplitude of 1 and 2 mm., respectively, which persisted for 24 minutes. The average preliminary blood sugar values were as follows: in those animals in which increased intestinal activity followed the administration of dextrose, 88 mg.; in the one in which there occurred no change in activity of the intestine, 40 mg.; and in the one in which a decrease in intestinal activity occurred, 48 mg. per hundred cubic centimeters of blood.

Ninety-Six Hour Obstruction.—Five observations were made. The length of time by which the administration of insulin preceded the observations varied between 36 and 93 minutes; in the majority of instances it was between 35 and 45 minutes. The time that elapsed between the administration of dextrose and changes in intestinal activity varied from 1 to 50 minutes. In two instances, previous injections of dextrose had been made. In each instance, 40 units of insulin was employed. In two instances, 50 cc., and in three instances, 75 cc., of 10 per cent dextrose solution followed the injection of insulin. There was an increase of blood sugar in each instance from a normal average of 74 mg. to 174 mg. per hundred cubic centimeters of blood (139 per cent increase). In three (60 per cent) of the instances, there was an increase in intestinal activity with average increases in tone and amplitude of 7 and 2 mm., respectively. The average duration of this increased activity was 4.5 minutes. In two (40 per cent) instances, no change in intestinal activity followed the infusion with dextrose.

RÉSUMÉ OF OBSERVATIONS

In comparing the effects produced by insulin and dextrose on the motility of the normal intestine and that which had been obstructed for varying periods of time, it was found that the difference in the reactions of the normal and the obstructed intestine to these substances was less marked than would possibly be supposed.

The effects of dextrose alone on the normal and the obstructed intestine were compared. In each instance observed there was a decrease in intestinal activity. There was apparently a less marked decrease in the activity of the intestine obstructed for longer than 24 hours than in that of the normal and that of the 24 hour-obstructed intestine. The average decreases in intestinal tone in the normal and in the 24 hour-obstructed intestine were 27.2 and 38 mm., respectively, as compared with 15 and 10 mm. in the 48 hour and 72 hour obstructions, respectively. Similar but less marked changes occurred in the amplitude of intestinal movement. This would indicate that the depressing effect of dextrose on intestinal activity is more marked in the normal and in the 24 hour-obstructed intestine than in the one that has been obstructed for longer periods of time.

A comparison of the effects of insulin alone on the normal and the obstructed intestine seems to indicate that increased activity occurs

more frequently in the normal intestine and that obstructed for 24 hours than in the one that has been obstructed for longer periods of time. An increase in activity occurred in 100 per cent (1 case each) in both the normal intestine and that obstructed for 24 hours, whereas an increase occurred in 40 per cent, 43 per cent and 66 per cent of those with 48, 72 and 96 hour obstructions, respectively. The number of observations made with the normal intestine and with that obstructed for 24 hours is, however, too small from which to draw definite conclusions. These observations would seem, however, to indicate that the normal intestine and that obstructed for 24 hours are more sensitive to the action of insulin than is the one in which an obstruction has existed for longer periods of time.

The reaction of the normal intestine to the administration of dextrose and insulin combined apparently did not differ from that occurring in one that had been obstructed for varying periods of time.

There was apparently some difference in the reactions of the normal and the obstructed intestine to insulin preceded by dextrose, not as regards the change in activity, but as regards the character of this activity. In those cases in which increased activity (increase in tone) occurred, it was greater in the normal intestine and in that obstructed for 24 hours than in the one that had been obstructed for longer periods of time. The average increases in tone in the normal and the 24 hour-obstructed intestine were 39 and 20 mm., respectively, whereas in 48, 72 and 96 hour obstructions, the average increases in tone were 13.5, 2.5 and 3 mm., respectively.

In comparing the effects that dextrose preceded by insulin had on the normal and the obstructed intestine, it is apparent that increased intestinal activity, as evidenced by increase in tone and amplitude, is more marked in the normal and the 24 hour-obstructed intestine than in the one obstructed for longer periods of time. The average increases in tone in the normal and the 24 hour-obstructed intestine were 46 and 50 mm., respectively, whereas the average increases in 48, 72 and 96 hour obstructions were 18, 22 and 7 mm., respectively. Suggestive similar differences exist as regards increases in amplitude, which, however, are less marked.

Of all the observations made concerning the effects of insulin on the activity of the normal and the obstructed intestine, 55.5 per cent concerned an increase in intestinal activity; 38.8 per cent, no change, and 5.5 per cent, a decrease in activity. In those instances in which an increase in activity occurred, there were average increases in tone and amplitude of 7.2 and 3.8 mm., respectively. The average duration of time of this increased activity was 6.1 minutes. In the one instance in which a decrease in activity occurred, there was a decrease in tone of 10 mm., which persisted for 47 minutes. In each instance there was

a decrease in blood sugar from an average normal value of 118 mg. to 75 mg. per hundred cubic centimeters (36 per cent decrease). It may be significant that the original average blood sugar value in those instances in which increased activity occurred was 129 mg. per hundred cubic centimeters of blood as compared with 96 mg. and 112 mg., respectively, in those in which there occurred no change and those showing a decrease in activity.

TABLE 6.—*Summary Showing the Effect of Insulin and Dextrose Separately or in Various Combinations on the Activity of the Intestine*

Nature of Injection; Number of Observations	Intestine			Blood	
	Increase	No Change	Decrease	Increase	Decrease
Insulin alone; 17........	55.5% T 7.2; A 3.8; T′ 6.1 B 129; B′ 84; —27%	38.8% B 96; B′ 47; —51%	5.5% T 10; A 0; T′ 47 B 112; B′ 62; —44.6%	0	100% B 118; B′ 75; —36%
Dextrose alone; 16......	....	....	100% T 22.9; A 6.9; T′ 8++ B 135; B′ 260; +92%	93% (13) B 126; B′ 269; +113%	7% (1) B 250; B′ 149; —40%
				B 135; B′ 260; +92%	
Dextrose and insulin; 10	44.5% T 2; A 2; T′ 2 B 121; B′ 76; —37%	55.4% B 92; B′ 75; —18%	....	25% (2) B 81; B′ 102; +26%	75% (6) B 110; B′ 80; —27%
				B 103; B′ 79; —23%	
Insulin preceded by dextrose; 10	70% T 12.3; A 3.3; T′ 9 B 187; B′ 95; —49%	30% B 162; B′ 63; —61%	....	....	100% (9) B 178; B′ 89; —50%
Dextrose preceded by insulin; 39	70% T 27; A 8.5; T′ 8+ B 92; B′ 221; +140%	19% B 76; B′ 205; +164%	10.8% T 3.5; A 2.5; T′ 10 B 98; B′ 184; +88%	94.8% (34) B 89; B′ 229; +156%	5.5% (2) B 104; B′ 86; —13%
				B 89; B′ 216; —129%	

The number of dogs in which there was an increase, no change or a decrease in activity of the intestine is expressed in percentage. The average increases in tone (T) and amplitude (A) of intestinal movement are expressed in millimeters. Time (T′) is given in minutes. The average blood sugar values before (B) and after (B′) the administration of insulin and dextrose in milligrams, with the precentage of gain or loss.

Of sixteen observations concerning the effects of the intravenous administration of dextrose solution on the activity of the normal and the obstructed intestine, 100 per cent concerned a decrease in activity, the average decreases in tone and amplitude being 22.9 and 6.9 mm., respectively. The average duration of the decrease in activity was more than 8 minutes. In thirteen of the fourteen instances (93 per cent), there was an increase in blood sugar from an average normal value of

126 mg. to 269 mg. per hundred cubic centimeters (113 per cent increase). In only one instance was there a decrease in blood sugar. The blood sugar for the entire group was increased from an average normal value of 135 mg. to 260 mg. per hundred cubic centimeters of blood (92 per cent increase).

Ten observations were made on the effects of dextrose and insulin combined on the normal and the obstructed intestine. In 44.5 per cent the activity of the intestine was increased, whereas in 55.4 per cent there was no change. In those instances in which an increase in activity occurred, there were average increases in tone and amplitude of 2 and 2 mm., respectively. The duration of the increased activity was 2 minutes. In six (75 per cent) of the observations, there were decreases in blood sugar from an average normal of 110 mg. to 80 mg. per hundred cubic centimeters (27 per cent decrease). In only two (25 per cent) was there an increase in blood sugar. It is possibly significant that the average blood sugar value in the group in which increased intestinal activity followed the administration of dextrose and insulin was 121 mg. as compared with 92 mg. in the group in which there occurred no change in intestinal activity.

Ten observations were made concerning the effects of insulin preceded by dextrose on the normal and the obstructed intestine. In 70 per cent there was an increase in intestinal activity, whereas in 30 per cent there was no change. In those instances in which there was increased activity, the intestinal tone and amplitude of movement were increased 12.3 and 3.3 mm., respectively. The average duration of this increased activity was 9 minutes. In every instance there was a decrease in blood sugar from an average normal value of 178 mg. to 89 mg. per hundred cubic centimeters (50 per cent decrease). The average blood sugar value in the group in which increased activity occurred was 187 mg. as compared with 162 mg. in the group in which no change in activity occurred.

Thirty-nine observations were made concerning the effects of dextrose preceded by insulin on the normal and the obstructed intestine. In 70 per cent, there was an increase in activity, consisting of average increases in tone and amplitude of 27 and 8.5 mm., respectively. The average duration of the increase in activity was 8 minutes. In 19 per cent there was no change in activity, and in 10.8 per cent there was a decrease in activity, consisting of decreases in tone and amplitude of 3.5 and 2.5 mm., respectively. The average duration of the decreased activity was 10 minutes. In 94.8 per cent of the instances, there was an increase in blood sugar from an average normal value of 89 mg. to 229 mg. per hundred cubic centimeters (156 per cent increase). In only 5.5 per cent was there a decrease in blood sugar. There was less difference noted between the preliminary blood sugar in those animals

in which an increase, no change or a decrease of intestinal activity occurred than was seen in other experiments. The average values of the preliminary blood sugar were as follows: dogs with increased activity of the intestine, 92 mg.; those in which no change occurred, 76 mg., and those in which a decrease in activity of the intestine resulted, 98 mg. per hundred cubic centimeters of blood.

COMMENT

In view of the results obtained in the present investigation concerning the effects of dextrose and insulin on the motility of the normal and the obstructed intestine, and the results of previous investigators concerning the effects on the motility of the stomach and the colon, it is suggested that dextrose alone, either as a preoperative or as a postoperative measure, should be employed cautiously, as without any exception in the present investigation the intravenous administration of dextrose solution produced a decrease in intestinal activity. The importance of the inhibiting effect of dextrose is probably more apparent than real, for, in the present investigation, even though the decreased intestinal activity averaged longer than 8 minutes, it is probable that in the majority of instances the hyperglycemia produced by the intravenous administration of dextrose solution will be controlled by sufficient autogenous insulin (produced by the pancreas) to compensate for the increased quantity of sugar (Sweeney,[14] Escudero,[15] Quigley, Hallaran and Barnes.[16] That the intravenous administration of dextrose exerts an inhibiting effect on the motility of the intestine is an important clinical fact. Even though in a normal person such inhibition may be of little practical importance, in one with an impending ileus or one in whom intestinal motility is not active, the intravenous administration of dextrose solution may cause paresis of the bowel. The results of the present investigation suggest that the administration of insulin with dextrose solution not only will prevent the inhibiting action of the dextrose but will actually increase the activity of the intestine. This effect is apparently most marked if the dextrose infusion is preceded by a preliminary administration of insulin. The administration of insulin alone, either preoperatively or postoperatively in a nondiabetic patient, however, is probably not justified clinically, because of the danger of producing hypoglycemic shock. If this method is employed, it should be used extremely cautiously, and then one should be guided by blood

14. Sweeney, J. S.: Dietary Factors That Influence the Dextrose Tolerance Test, Arch. Int. Med. **40**:818 (Dec.) 1927.

15. Escudero, P.: Latent Diabetes, Endocrinology **11**:27, 1927.

16. Quigley, J. P.; Hallaran, W. R., and Barnes, B. O.: Variations in Blood Sugar Values of Normal and Vagotomized Dogs Following Glucose Administration, J. Nutrition **5**:77 (Jan.) 1932.

sugar determinations. The inhibiting action of dextrose solutions is not due to the hypertonicity of the solutions, because it has been demonstrated repeatedly, both experimentally and clinically, that intravenous administration of hypertonic salt solution stimulates rather than inhibits the intestine. That hyperglycemia itself is not responsible for the inhibiting effect that dextrose solution has on intestinal activity is evidenced by the difference in the results obtained in those cases in which the administration of dextrose solution was preceded by that of insulin. In the latter cases there was an increase in activity in 70 per cent, with average increases in tone and amplitude of 27 and 8.5 mm., respectively, whereas in the former cases there was a decrease of activity in every instance, with average decreases in tone and amplitude of 22.9 and 6.9 mm., respectively. The lack of correlation between the blood sugar values and the activity of the intestine substantiated the contention that the inhibiting effect of dextrose solution is not due to simple hyperglycemia. Of interest, however, is the fact that rather consistently in the present investigation a more marked increase in intestinal activity occurred following the administration of insulin either alone or in combination with dextrose when the original blood sugar values were high. With but few exceptions, the administration of insulin produced an increase in activity of the intestine in those animals with relatively high blood sugar values, whereas either no change or a decrease in activity occurred in those animals with originally relatively low blood sugar values. The exact mechanism of the inhibiting effect of dextrose alone and the stimulating effect of insulin alone or combined with dextrose is not known. Some investigations [17] indicate that the changes are produced by impulses passing over the vagi. In the present investigation, no attempt was made to determine the part played by the nerve supply in the intestine. Because of the lack of correlation between the blood sugar values and intestinal activity, we are inclined to believe with Quigley and Templeton [7] that alterations in the cell metabolism may occur as a result of the administration of dextrose and insulin before blood sugar changes occur. It is probably for this reason that the most marked activity was obtained in those instances in which the administration of dextrose was preceded by that of insulin. In such cases not only was there an increase in intestinal activity in the majority of observations but also the character of the reaction was marked.

The fact that more prompt response in intestinal activity occurred in the normal intestine and that which had been obstructed for 24 hours than in the intestine that had been obstructed for longer periods of time (48, 72 and 96 hours) is significant. Less significant changes in activity

17. Quigley, Johnson and Solomon.[5]   Templeton and Quigley.[6]   Quigley and Templeton.[7]   Quigley and Templeton.[8]   Wilder and Schlutz.[9]

occurred in the intestine that had been occluded for 48 hours or longer, probably because of alterations in the metabolism of muscle cells in the wall of the intestine or because of changes in the cells produced by dilatation of the intestine and possibly toxemia. As a result of these alterations, the irritability and the response to various stimuli including dextrose and insulin may be lowered.

Whether dextrose and insulin exert similar effects on the human intestine is difficult to say, because the exact changes occurring in the intestine are difficult to determine clinically. Careful observation of a large number of patients receiving dextrose and insulin, particular attention being paid to changes in intestinal activity, will be necessary before definite conclusions can be drawn concerning the clinical significance of the experimental observations. It is our own observation that patients with disease of the gallbladder or of the liver, to whom dextrose has been administered because of damage to the liver have had more abdominal distention and not as smooth a convalescence as those with other abdominal lesions. We have always attributed this to operative manipulation of the upper part of the abdomen, but it is possible that the administration of dextrose may have been at least partially responsible for the distention. In the present investigation, much larger doses of insulin (from 10 to 40 units) were employed than would be justified clinically. One should probably never use more than 1 unit of insulin for every 2 Gm. of dextrose. The doses of dextrose used were much smaller (from 1 to 10 Gm.) than those generally employed clinically. This fact may be of clinical significance, for apparently in those instances in which large doses were used the inhibiting effect of dextrose alone was more marked than when smaller amounts were given.

SUMMARY AND CONCLUSIONS

1. Experimentally dextrose and insulin either alone or in various combinations produced marked changes in the activity of the normal and the obstructed intestine.

2. The changes were more marked in the normal intestine and that which had been obstructed for 24 hours than in the one obstructed for longer periods of time (48, 72 and 96 hours).

3. Insulin alone produced an increase in intestinal activity (both in the normal and in the obstructed intestine) in 55.5 per cent, the average increases in tone and amplitude being 7.2 and 3.8 mm., respectively.

4. Dextrose alone caused an inhibition of intestinal activity (both in the normal and in the obstructed intestine) in every instance (100 per cent), the average decreases in tone and amplitude being 22.9 and 6.9 mm.. respectively.

5. Dextrose and insulin combined resulted in an increase in intestinal activity in 44.5 per cent and no change in 55.4 per cent.

6. Insulin preceded by dextrose produced an increase in intestinal activity in 70 per cent and no change in 30 per cent. The average increases in tone and amplitude were 12.3 and 3.3 mm., respectively.

7. Dextrose solution preceded by insulin produced an increase in intestinal activity in 70 per cent, with average increases in tone and amplitude of 27 and 8.5 mm., respectively. In 19 per cent there was no change, and in 10.8 per cent there was a decrease in activity.

8. The experimental results indicate that dextrose solution exerts an inhibiting effect on both the normal and the obstructed intestine which can be largely obviated by the use of insulin. It is suggested that clinically dextrose alone be used cautiously, and that it be combined with insulin in order to minimize the inhibiting effect it may have on the intestine.

EFFECT OF ALKALIS ON EXPERIMENTAL PEPTIC ULCER

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AND

HENRY H. RUBIN, M.D.

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The use of alkalis in the treatment of peptic ulcer is based on the assumption that the complete neutralization of hydrochloric acid by the administration of alkalis renders gastric peptic digestion inactive, and the granulation tissue of the ulcer heals.

The purpose of the present study was to determine the effect of the administration of alkalis on experimental peptic ulcer as produced by Mann and Williamson.[1] These observers were able to produce ulcers in dogs by surgical duodenal drainage; i. e., the junction of the pylorus and duodenum was severed and the duodenal end closed. The duodeno-jejunal angle was located, and the jejunum was followed down for a distance of from 10 to 15 cm., at which point it was transected. The proximal end of the jejunum was anastomosed into the terminal portion of the ileum from 20 to 30 cm. from the cecum by means of an end-to-side anastomosis. The distal end was sewed to the pylorus. Ulcer occurred at the site of the junction with the pylorus in from one day to three weeks. These dogs lived from one day to several months.

Healing of the experimental ulcer was brought about by Mann[2] by occlusion of the pyloric opening proximal to the ulcer, which prevented the passage of the gastric contents over it, and the stomach was drained by means of gastrojejunostomy, the stoma in the jejunum being from 25 to 30 cm. from the ulcer. Mann found also that the drainage of the duodenal secretions back into the ulcer-bearing loop of the jejunum caused healing. The rate of healing was slower and the process more irregular as compared to the other procedure in which the ulcer was completely protected from the gastric secretions. The dogs lived from ten to fifteen days after the operation in most instances. However, some lived from twenty to thirty days thereafter.

As far as we can determine, no attempt has been made to bring about healing of this type of ulcer by medical means.

1. Mann, F. C., and Williamson, C. S.: Ann. Surg. 77:409, 1923.
2. Mann, F. C.: S. Clin. North America 5:753 (June) 1925.

Morton [3] was able to study the reparative process of these ulcers roentgenologically following gastro-enterostomy.

Dragstedt and Vaughn [4] found that alkalis in amounts sufficient to neutralize gastric secretions promote the healing of experimental gastric ulcers. They produced these ulcers by injecting 4 per cent silver nitrate into the gastric mucosa and then placing from twenty to thirty sutures of heavy linen thread in this area; the sutures, extending through the muscularis, were tied loosely and the cut ends permitted to extend into the lumen of the stomach. In four of six dogs chronic ulcers developed three and four months after operation. Then various combinations of sodium bicarbonate, calcium carbonate and magnesium oxide were given, with the aforementioned results.
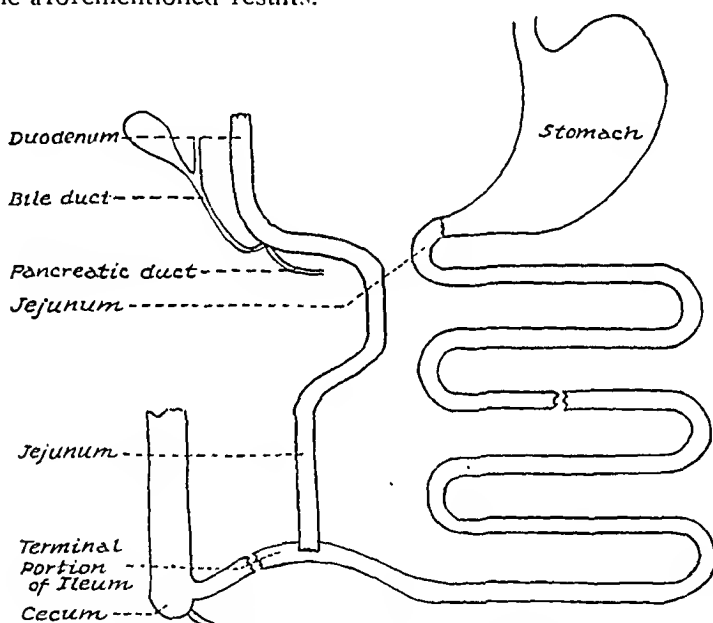
Fig. 1.—Diagram showing operative field.

EXPERIMENTATION

Method.—Peptic ulcers were produced in dogs by surgical duodenal drainage as described by Mann and Williamson (fig. 1). The dogs were reoperated on about three weeks later in order to demonstrate the presence of an ulcer. As soon as they had recovered from the effects of this exploratory operation, feeding of alkalis was begun. Calcium carbonate was chiefly employed. In three instances a combination of sodium bicarbonate, calcium carbonate and magnesium oxide was used. In order to determine whether alkalosis developed, the carbon dioxide

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3. Morton, C. B.: Ann. Surg. **85**:207 (Feb.) 1927.
4. Dragstedt, L. R., and Vaughn, A. M.: Arch. Surg. **8**:791 (May) 1924.

Dog	Date of Operation	Date of Reoperation	Presence of Ulcer	Medication, Amount Used	No. Days Feeding	Date of Death	No. Days Alive after Reoperation	Comment	Postmortem Findings
1	3/15	4/11	+	0	0	4/21	10	Control	Perforating ulcer, peritonitis
2	6/ 1	6/21	+	0	0	6/26	5	Control	Perforating ulcer, peritonitis
3	4/30	5/21	+	0	0	7/31	71	Control	Perforating ulcer, peritonitis
4	6/25	7/16	+	0	0	9/ 4	50	Control	Perforating ulcer, peritonitis
5	7/22	8/12	0	0	0	Killed 1/14 CO gas	147	Control	No ulcer
6	9/ 3	9/24	+	1% HCl, 300 cc. daily	43	11/17	54	....	Perforating ulcer, peritonitis
7	9/10	10/ 1	+	1% HCl, 300 cc. daily	87	Killed 1/14 CO gas	105	....	Round ulcer present, adherent to adjacent duodenum with perfect walling off
8	3/10	4/13	+	Calcium carbonate, 180 grains daily	9	4/27	14	Blood chemistry: CO₂, 51 cc. per 100 cc. plasma	Perforating ulcer, peritonitis
9	3/13	4/17	0	Calcium carbonate, 180 grains daily	49	Killed 9/5 CO gas	141	Gastric analysis: 6/13, no acid; 6/14, free 13, total 68; 6/15, free 24, total 33. Blood chemistry: 5/17, CO₂, 30 cc. per 100 cc. plasma	No ulcer
10	4/13	5/ 7	+	Calcium carbonate, 180 grains daily	22	6/ 5	29	Blood chemistry: 5/7, CO₂, 55 cc. per 100 cc. plasma	Perforating ulcer, peritonitis
11	4/26	5/17	+	Calcium carbonate, 180 grains daily	23	6/15	29	Blood chemistry: 5/17, CO₂, 33 cc. per 100 cc. plasma. Gastric analysis: 6/13, no acid; 6/14, free 0, total 23	Perforating ulcer, peritonitis
12	5/14	6/16	+	Magnesium oxide, sodium bicarbonate, calcium carbonate, 90 grains of each	24	7/22	36	....	Perforating ulcer, peritonitis
13	10/30	11/19	+	Magnesium oxide, sodium bicarbonate, calcium carbonate, 100 grains daily of each	6	12/ 1	12	....	Perforating ulcer, peritonitis
14	12/24	1/14	÷	Magnesium oxide, sodium bicarbonate, calcium carbonate, 100 grains daily of each	22	2/13	30	Blood chemistry: 1/19, CO₂, 35 cc. per 100 cc. plasma; 2/6, CO₂, 50 cc. per 100 cc. plasma	Perforating ulcer, peritonitis

content of the blood was determined in several instances. Determinations of the gastric acidity were also made in certain instances.

The amount of alkali and the period of time over which it was given appear in the table.

Two dogs received 300 cc. of 1 per cent hydrochloric acid.
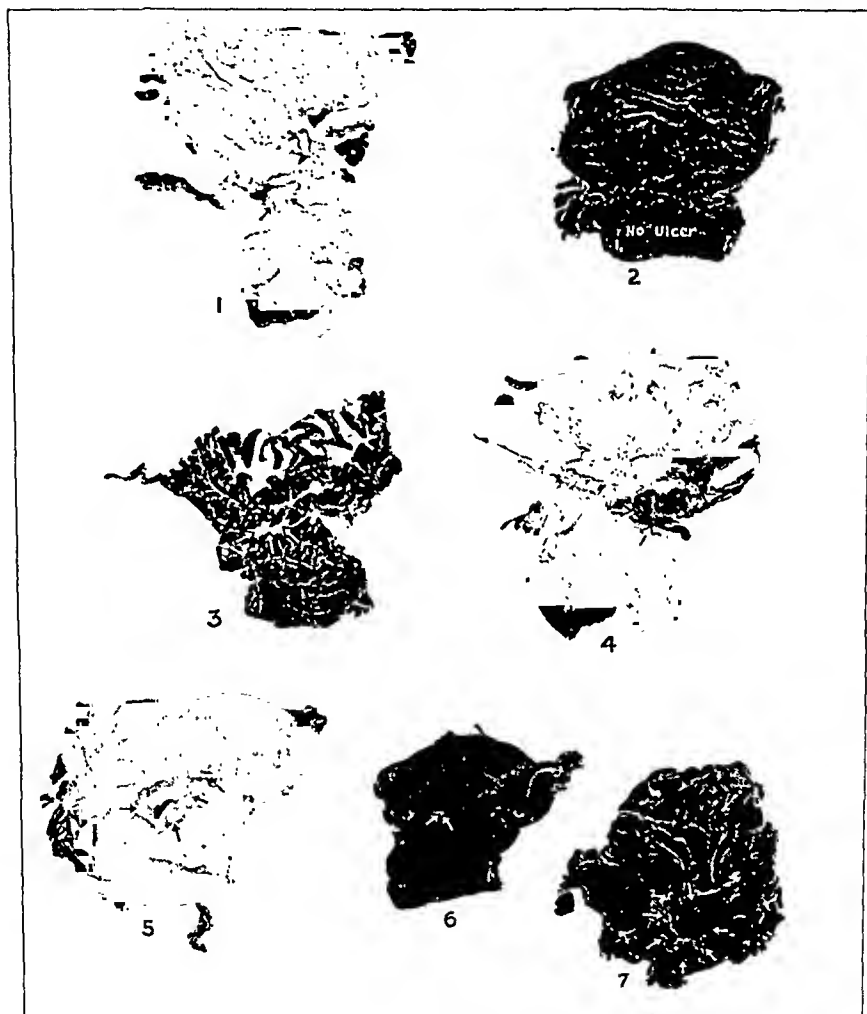
Fig. 2.—Sections showing ulcers and perforation.

Observation and Results.—The total number of dogs operated on was sixty-four. Of these, fourteen survived the first operation. These were used for experimental purposes. In all except two of the fourteen dogs a typical peptic ulcer could be felt and demonstrated at the time of the secondary operation. Dogs 1, 2, 3, 4 and 5, used as controls, received no alkali and lived ten, five, seventy-one, fifty and one hundred and

forty-seven days respectively, after the secondary operation. In dog 5, however, an ulcer did not develop. Seven dogs receiving alkali lived from twelve to thirty-six days following the demonstration of the ulcer. Three of these dogs receiving a combination of approximately 100 grains (6 Gm.) each of sodium bicarbonate, magnesium oxide and calcium carbonate lived thirty-six, twelve and thirty days and were in good physical condition. Of the other four dogs, which received 180 grains (11 Gm.) of calcium carbonate, three lived fourteen, twenty-nine and twenty-nine days, and one that had no ulcer lived for one hundred and forty-one days. The ulcers at autopsy showed no evidence of healing, and death was due to perforative peritonitis. Two dogs were given 300 cc. of 1 per cent hydrochloric acid; one lived fifty-four days, and the other was killed with carbon monoxide gas at the end of one hundred and five days. The first dog died of perforative peritonitis and the second dog showed a healed ulcer walled off by the duodenum.

Chemical examination of the blood did not reveal the presence of alkalosis in any instance. The normal carbon dioxide content of the blood of the dog is between 40 to 50 cc. per hundred cubic centimeters of plasma.

On dog 11 gastric analyses were made a few days before death. No acidity was found on two occasions. In dog 9, in which an ulcer did not develop and which received the same amount of alkali as dog 11, the first analysis showed no acidity, the second analysis on the day following showed 31 degrees of free acidity and 68 of total acidity, and the third analysis a day later revealed 24 degrees of free acidity and 33 of total acidity.

In every animal that died postmortem examination showed a perforated peptic ulcer with generalized peritonitis.

SUMMARY

An attempt was made to study the effect of alkalis on experimentally produced peptic ulcers. The results do not support the view that alkalis are a factor in aiding the healing of ulcer. The dogs receiving alkali did not live longer than the controls that received no alkali. The end-results were the same, perforation and peritonitis occurring in all. The administration of large amounts of 1 per cent hydrochloric acid apparently had no influence in hastening the perforation of the ulcers.

REACTIONS OF THE RAT TO AVERTIN CRYSTALS, AVERTIN FLUID AND AMYLENE HYDRATE

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Avertin (tribromethanol) was first introduced for clinical use as a crystalline preparation to be administered rectally as a 2.5 to 3 per cent solution in distilled water. The low solubility of the preparation in water (3.5 per cent at 40 C.) necessitates the rectal administration of relatively large volumes of fluid. At temperatures above 40 C. solutions of avertin decompose into hydrobromic acid and dibromacetaldehyde. Owing to these disadvantages, avertin fluid has largely displaced the aqueous solutions for clinical uses.

Avertin fluid contains in each cubic centimeter 1 Gm. of avertin crystals and 0.5 cc. (407.5 mg.) of tertiary amyl alcohol (amylene hydrate). This preparation is said to be more stable than the aqueous solutions of avertin, and the amylene hydrate has been reported to accelerate the rate of absorption of the solute from the rectum. In addition, since the solvent alone is somewhat hypnotic, the combination of avertin and amylene hydrate might result in a summative action; i. e., the solvent, according to Raginsky, Bourne and Bruger,[1] adds to the sedative and anesthetic properties of avertin.

The literature on avertin is extensive, but in practically all of the experimental work and in the majority of the clinical studies a watery solution of the avertin crystals has been used rather than avertin fluid. During the course of another study distinct differences between the effective or sedative dosages of the crystalline or aqueous forms, and the fluid or amylene hydrate solutions of avertin were observed in rats. These observations were at variance with the statements of Raginsky, Bourne and Bruger regarding the results in the dog and in man.

METHODS

Normal adult albino rats were used in all experiments. The "complete sedative action" was determined by recording the tranquilizing effects of the several preparations on the spontaneous movements of the rat when tied down on an animal board. Details of the method have been published elsewhere.[2]

1. Raginsky, B. B.; Bourne, W., and Bruger, M.: J. Pharmacol. & Exper. Therap. **43**:219, 1931.

2. Barlow, O. W.: The Tranquilizing Potency of Morphine, Pantopon, Codeine, Papaverine and Narcotine: Results of Tests on the Rat, J. A. M. A., **99**:986 (Sept. 17) 1932.

The premedication dosage was determined by gradually increasing the doses until the animals could be maintained in a reflex-free state for at least thirty minutes in an atmosphere containing 85 per cent of nitrous oxide and 15 per cent of oxygen.

The narcotic or completely anesthetic dosage was considered as that which rendered the animals reflex-free. The most suitable index found was inhibition of the reaction to pain when the hind feet were pinched with a hemostat.

The lethal dosages were determined on a relatively large series of rats because of the marked variability in the reactions of different animals to avertin fluid and to amylene hydrate. The lethal dose was considered as that which kills at least seven of a minimum series of eight animals within six hours with avertin or avertin fluid, or within fourteen hours with amylene hydrate. No differentiation between early and late deaths was deemed necessary.

The preparations were injected either subcutaneously or rectally. The avertin crystals were dissolved in distilled water and administered in a 2.5 to 3 per cent solution. The avertin fluid was administered as 25 to 100 per cent solutions of avertin in amylene hydrate. The amylene hydrate was administered either as an 8 per cent aqueous solution or undiluted.

RESULTS

The table illustrates for the three preparations the observed sedative premedication, narcotic and lethal dosages, as well as the time of induction and duration of sleep and time until complete recovery with sublethal doses and the time until death with lethal dosages. The survivals (O) and deaths (+) with various dosages are illustrated in the chart.

Avertin Crystals, Subcutaneous Administration.—The ratio of the sedative, premedication and narcotic to the lethal dosage was 0.39, 0.58 and 0.62 : 1, respectively. The margin between the sedative and the premedication dose was wide, and intermediate doses produced moderate to deep anesthesia, but complete elimination of the reaction of pain (strong pressure on the foot with a hemostat) required a dose of 450 mg. per kilogram of body weight.

The time of induction was very short, i. e., within from one and one-half to three minutes, and the medium duration of sleep was less than one hour but varied from six-tenths to one and three-tenths hours. Complete recovery required approximately two and one-half hours. Death following the injection of lethal doses usually occurred within one and one-fourth hours, but varied from eight-tenths to two hours.

Rather marked variability between the reactions of different animals to the same dose was noted. Lethal reactions were observed with only 83 per cent of the usual lethal dose, and recoveries occurred exceptionally with doses well above the amount usually lethal.

Avertin Fluid, Subcutaneous Administration.—The reactions to avertin fluid differed markedly from a quantitative standpoint from those noted following the injection of a similar dose of avertin in an aqueous solution. With avertin fluid, the time of induction and duration

Effects of Avertin and Amylene Hydrate on the Rat

Preparation	Mode of Administration	Dose in Mg. per Kilogram of Body Weight				Onset of Sleep with Anesthetic Dose, Minutes		Duration of Action with Anesthetic Dose, Hours				Time of Death with Lethal Doses, Hours	
		Completely Sedative	Premedication N₂O-O₂	Complete Narcosis§	Lethal¶			Sleep		Complete Recovery			
						Average	Range	Average	Range	Range	Average	Range	Average
Avertin crystals 2.5-3% watery solution	Subcutaneous lower abdominal quadrant	275	420	450	730	2.5	1.5-5	0.9	0.6-1.3	1.5-3.5	2.5	0.8-2	1.25
Avertin fluid 1 cc. = 1 Gm. of avertin*	Subcutaneous lower abdominal quadrant	660	960	>960	1,400	35	20-65	2.0	1.5-4.0	1.5->24	5.75	1.2-3.5	1.75
Amylene hydrate	Subcutaneous lower abdominal quadrant	900	1,050-1,100	1,130	1,400	45	45-120	5.0	4.5-12	10->24	12.0	7-11	9.0
Avertin crystals watery solution	Subcutaneous on one side	275	420	450	730	2.5	1.5-6	2.2	1.5-7	4.5-18	>6	0.4-2.3	1.3
Amylene hydrate†	Subcutaneous opposite side												
Avertin crystals, watery solution‡	Rectal	...	420	550	660-730	3.5	1.5-6	1.1	0.4-1.6	1.5-3	2.2	0.8-1.5	0.9
Avertin fluid	Rectal	325	450	>480	1,375	12	5->20	1.45	1.5-2.2	3.5-24	4.5	0.9-2.2	1.75
Amylene hydrate#	Rectal	...	825	980	1,220	35	20-50	3.5	3.5-5	10->24	12.0	2.5-12	4.0

* 1 cc. of avertin fluid contains 1 Gm. of avertin crystals and 0.5 cc. (407.5 mg.) of amylene hydrate.
† The dose of amylene hydrate, injected separately, was adjusted to that of the avertin crystals, so as to be equivalent to the amount of avertin in avertin fluid.
‡ Data from Tunger.
# Data from Tunger, extended by Barlow.
§ Narcosis was indicated by absence of reaction of pain to pinching feet.
¶ The lethal dose was taken as that which killed at least seven of a minimum series of eight animals.

of sleep and time until complete recovery were markedly prolonged, and the production of a standard reaction, for instance, sedation or narcosis, required considerably higher doses.

The sedative and premedication doses of avertin fluid were two and four-tenths and two and three-tenths times the doses of avertin crystals,

Chart showing survivals and deaths with different dosages.

and the doses required for narcosis or lethal reactions were approximately twice those of the crystals, in spite of the fact that the lethal dose of avertin fluid contains, in addition to 1,400 mg. of avertin crystals, 41 per cent of the minimum lethal dose of amylene hydrate. The variability in the reactions to the amylene hydrate solution of avertin was also markedly greater than in the case of the watery solution.

Amylene Hydrate, Subcutaneous Administration.—Amylene hydrate subcutaneously produces transient irritation, local hemolysis and edema, but no caustic action or slough was observed. The doses required for sedative or complete narcotic effects are quite large, and the margin between the sedative, narcotic and lethal doses is rather narrow.

The time of induction or onset of sleep which is an index of absorption was somewhat longer, while the duration of sleep and the time until complete recovery after narcotic doses or the time to death after lethal doses were from two and one-half to three times as long as was noted with avertin fluid. The lethal dose of amylene hydrate is about the same as that of avertin in the form of avertin fluid, which contains, in addition to avertin, 29 per cent of its weight of amylene hydrate.

The action of the amylene hydrate per se in the dosage ratio present in the completely narcotic dosage of avertin fluid given subcutaneously would result in moderate sedation, a 20 per cent increase in respiratory rate, a somewhat greater decrease in respiratory volume and a 35 per cent depression of minute volume.

Simultaneous Injection of Avertin and Amylene Hydrate.—Although avertin and amylene hydrate act in the same depressive direction, their combination in avertin fluid actually decreases the depression and toxicity for rats to half or less that of the watery solution, as was noted. The nature of this apparent contradiction of reactions was investigated by the subcutaneous injection of various doses of an aqueous solution of the avertin crystals into one abdominal quadrant and at the same time the injection into the opposite quadrant of the quantity of amylene hydrate present in an equal dose of avertin in the form of avertin fluid.

Animals given injections of avertin alone or of avertin and amylene hydrate at separate sites reacted alike so far as induction or depth of anesthesia or toxicity was concerned. The time to complete recovery was distinctly greater in the latter series and indicated that the effects of the longer acting amylene hydrate become apparent after those of the more evanescent avertin are passing off.

These data show that the diminished toxicity of avertin when it is mixed with amylene hydrate is not due to any physiologic antagonism, since it does not occur if the two preparations are injected at different sites. The toxic action must therefore be indirect, presumably by slowed absorption, the amylene hydrate retaining a large part of the avertin at the site of injection, because of the greater solution affinity, until the solvent itself is completely absorbed. The slow recoveries of surviving animals may perhaps involve an additional factor, namely, delayed urinary excretion, since hematuria was observed regularly after medication with moderate doses of either amylene hydrate or avertin fluid. However, this suggestion has not been investigated further.

Avertin Crystals. Rectal Administration.—The rectal administration of a 2.5 to 3 per cent aqueous solution of avertin is not satisfactory in the rat owing to the excessive volume required for studies of toxicity. However, no significant quantitative or qualitative differences in the responses to avertin were noted whether the avertin was administered subcutaneously or rectally. After rectal administration, the time of induction and duration of sleep were slightly longer and the range was wider than after the subcutaneous injection of similar doses. On the other hand, complete recovery from narcotic doses, or death from lethal doses, occurred slightly earlier after rectal than after subcutaneous injection.

Tunger [3] differentiated between the rectal dosages that produce early and late deaths. His fatal dosage for early deaths has been confirmed, but as the difference between the late and the early fatal dosage is only 9.6 per cent, the significance of such a differentiation is questionable. In the present study, fatal reactions occurred within one and one-half hours as a rule; so only early deaths are considered primary.

Avertin Fluid, Rectal Administration.—The sedative, premedication and narcotic doses of avertin in amylene hydrate for rectal administration were between 20 and 25 per cent greater than those required when distilled water was used as the solvent.

These data indicate that small to moderate doses of avertin fluid are distinctly more effective when given by rectum than on subcutaneous injection. The effectiveness of avertin fluid rectally in such doses approaches that of an aqueous solution of the crystals. This greater efficiency of avertin fluid by rectal as compared with subcutaneous administration does not hold for fatal doses, for the fatal doses by the two routes are practically identical in effect. Rectal administration of avertin fluid gives, therefore, a much wider margin of safety between the narcotic and the fatal dose than does subcutaneous administration. This may be explained by the assumption that the absorption of the smaller doses of amylene hydrate is much more rapid from the rectal than from subcutaneous injections, but that, with larger doses, the rectal rate of absorption becomes slowed to that of the subcutaneous injection, and avertin is retained by solution affinity. The matter has not been tested directly, but that amylene hydrate slows the rectal absorption of avertin is indicated by the slower onset of sleep, the wider range of reactions and the longer duration of sleep. Complete recovery from avertin fluid was somewhat earlier (20 per cent) after rectal than after subcutaneous injection, but the duration of action, irrespective of

3. Tunger, H.: Arch. f. exper. Path. u. Pharmakol. **160**:74, 1931.

the mode of administration, was markedly longer than after the development of a similar reaction by means of an aqueous solution of the crystals.

Amylene Hydrate, Rectal Administration.—The rectal dosage of amylene hydrate is slightly (from 13 to 14 per cent) less, the absorption rate is somewhat more rapid and the duration of action is correspondingly shorter than when the preparation is administered subcutaneously. The differences observed were not significant.

CONCLUSIONS

1. The sedative, premedication, anesthetic and lethal doses of avertin crystals, avertin fluid and amylene hydrate have been compared, following both subcutaneous and rectal administration to the rat.

2. The effectiveness and toxicity of an aqueous solution of avertin are markedly greater than those of equal doses of avertin dissolved in amylene hydrate, i. e., avertin fluid. This difference in action is due to a distinct delaying effect of the solvent on the rate of absorption of avertin.

3. The time of induction is slower and the duration of action following the injection of avertin fluid is distinctly greater than after the development of an equal reaction by means of a watery solution of avertin.

4. The slow recovery after the administration of avertin fluid occurs also when the two ingredients are injected at different sites, and is therefore not explainable by delayed absorption; it must be attributed to the persistent depressive effect of the amylene hydrate.

SIMULTANEOUS RESPIRATORY EXCHANGE AND BLOOD SUGAR TIME CURVES

OBTAINED IN APPARENTLY NONDIABETIC PATIENTS WITH NONHEALING WOUNDS

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It is a well known fact that surgical wounds tend to heal slowly or not at all in the patient with uncontrolled diabetes. In this phenomenon, one of the surgeons at the Montreal General Hospital, Dr. A. T. Bazin, had the impression that an explanation might be found of nonhealing wounds met with in apparently nondiabetic patients and suggested an investigation of the carbohydrate metabolism in such cases. The experience with the first case so investigated was previously reported.[1] Briefly, the findings, as reported by Dr. Bazin, were as follows:

A female, aged 47, was admitted on Oct. 14, 1924, with an indolent ulcer on the dorsum of the right foot. In August she had suffered a slight abrasion of that area which became infected. The involved area rapidly spread and, in spite of active treatment, the skin sloughed over an area of 5 by 4 inches. After an interval a Thiersch graft was transferred from the thigh, but with no result except that she then had two ulcers instead of one, the thigh wound also failing to heal.

On admission, the ulcers presented an indolent appearance with pale flabby granulations and excessive discharge. The patient was somewhat obese, but otherwise the physical examination was negative in every particular. Repeated urinalysis failed to show any abnormality. The Wassermann test was negative. I taxed my ingenuity to stimulate healing, ringing the changes with various forms of dressings and applications and different modes of physiotherapy. The ulcer would heal almost completely when suddenly the new epithelium would melt away leaving the area of granulation about the same size as when first seen.

Finally, on January 13, two months after admission, an examination of the blood obtained in the fasting state showed a blood sugar of 0.161 per cent—a hyperglycæmia but below the normal urinary threshold. With regulation of the diet this promptly dropped to normal (0.08 per cent); the ulcers healed, and the patient was discharged on February 2, only twenty days after discovery and correction of the real cause of the delayed healing.

In this case, neither the history nor the signs and symptoms suggested diabetes, other than the slow healing of the wound. At no time was there any glycosuria. The patient was readmitted for examination on Dec. 2, 1931, approximately seven years later. There was, again, no

1. Bazin, A. T.: Canad. M. A. J. 23:146 (Aug.) 1930.

reason to suspect diabetes. On admission, in the fasting state, the urine was free from sugar and acetone bodies, the blood sugar was 0.116 per cent, and the plasma cholesterol was 0.187 per cent. On the following day, a blood sugar time curve was obtained, following the administration of 100 Gm. of dextrose, with the following results:

Time	Blood Sugar
Fasting state	0.114 per cent
30 minutes after dextrose	0.126 per cent
60 minutes after dextrose	0.116 per cent
120 minutes after dextrose	0.111 per cent
150 minutes after dextrose	0.100 per cent

Following this experience, analysis of the blood sugar has been a routine procedure in cases in which a similar condition has been suspected. A common finding is mild hyperglycemia, in spite of the fact that all examinations of the blood sugar are, as a routine, made in the morning in the fasting state, from twelve to fifteen hours after the last meal; the blood sugars usually range between 0.13 and 0.16 per cent. That these findings are not accidental may be seen from repeated analyses of the blood made at different intervals of time. The results in a case met with recently are cited as an example:

Date	Blood Sugar, per Cent	Time Interval Between Tests, Days
February 16	0.143	
17	0.139	1
19	0.131	2
22	0.137	3
29	0.140	7
March 7	0.140	14

Because of these experiences, when blood sugars during fasting were found normal in suspected cases, a more detailed study of the carbohydrate metabolism was made with the use of blood sugar time curves following the administration of dextrose. With this practice, it was found in many cases that, though the fasting blood sugars were normal, the curves indicated disturbed carbohydrate metabolism. Treatment of these patients with diet and insulin led, in the great majority of cases, to healing.

Because of routine precautions, technical error is excluded with respect to the estimation of blood sugar, and the routine method for obtaining blood sugar time curves has also minimized the vagaries of this test. It may be observed that merely giving a person 100 Gm. of dextrose by mouth and making examinations of the blood sugar at periodic intervals may lead to almost any type of curve—normal in the abnormal and abnormal in the normal person. A variety of precautions is essential. In addition to accuracy of the estimation of blood sugars, preparation of a palatable drink and accurately timed collections of blood

are among the many variables which have to be considered in the interpretation of such curves. Some of these were dealt with previously by Rabinowitch and Bazin.[2]

Prompted by these experiences in the surgical wards, the gynecologic service attempted to find an explanation for nonhealing wounds met with in cases of "birth trauma" and as a result of an intensive routine investigation, a fairly high incidence of the aforementioned condition was met with; though wounds failed to heal at the normal rate prior to treatment, with diet and insulin therapy, wounds would heal at the normal rate. That the number of such cases is appreciable is suggested by the fact that eighteen patients were discovered in this service during 1931 alone.

For some time, in spite of the experiences described, I was skeptical about the value of insulin in these cases. Since the discovery of insulin, there has been an increasing literature with respect to the use of this therapeutic agent in conditions other than diabetes. These conditions have included gastro-intestinal disturbances in children, postoperative vomiting, vomiting during pregnancy and others. More recently, insulin has been given as an antiemetic[3] and also has been advised in the treatment of gastric ulcer.[4] In 1928, Rabinowitch and Bazin[5] made a study of blood sugar and respiratory metabolism time curves of normal persons following the simultaneous administration of dextrose and insulin. From the results obtained, it was concluded that, unlike its effects on diabetic persons, insulin did not increase the rate of oxidation of administered carbohydrates in normal persons. As a matter of fact, a decreased rate was observed, and it was suggested that insulin not only does not enhance oxidation of sugar in the normal person, but, in some as yet unexplained way, interferes with the normal mechanism. The data seemed to fit in with those previously obtained by others in animal experiments. Macleod observed that there is a striking difference between normal and diabetic persons, and that the endogenous supply of insulin is always at an optimum in the normal animal.[6] The only reason, therefore, for the use of insulin in the present series of cases was that, though the patients did not appear to be diabetic, there was no doubt about some abnormality of the carbohydrate metabolism, and, though skeptical for some time, with the accumulation of a fairly large number of cases it would appear that the relationship observed between treatment and result was causal and not accidental.

2. Rabinowitch, I. M., and Bazin, A. T.: Ann. Surg. **94**:354, 1931.
3. Elias, H., and Violin, E.: Ztschr. f. d. ges. exper. Med. **59**:61, 1928.
4. Code, A., and Barral, P.: Monde méd., Paris **40**:497, 1930.
5. Rabinowitch, I. M., and Bazin, E. V.: J. Biol. Chem. **80**:723, 1928.
6. Macleod, J. J. R.: Carbohydrate Metabolism and Insulin, New York, Longmans, Green & Co., 1926.

It is of interest to observe that some of these patients were remarkably resistant to insulin. The usual dosage in such cases is 5 units every six hours, in accordance with our experiences with diabetes that small amounts of insulin given at frequent intervals control blood sugars much better than large amounts given at less frequent intervals. We now have a number of records at the hospital which show that some of these patients, though apparently not diabetic, were able to tolerate as much as 15 units of insulin every six or eight hours, that is, from 45 to 60 units of insulin a day, in spite of the absence of marked hyperglycemia; as previously stated, the blood sugars ranged between 0.13 and 0.16 per cent. We also had a number of cases showing resistance to the same doses of insulin, though the blood sugars obtained in the fasting state were normal. In these cases, the disturbed carbohydrate metabolism was detected by the use of blood sugar time curves.

In view of the foregoing observations, it was considered of interest to make a further study of the carbohydrate metabolism. The method employed was that which has been in use in this laboratory for a number of years. It was first applied in our laboratory to a study of renal glycosuria,[7] and since then has become a standard procedure, hundreds of such tests having now been made. The method consists of a simultaneous determination of blood sugar and respiratory metabolism time curves following the ingestion of dextrose. That it is an ideal method of studying carbohydrate metabolism may be seen from the following observations.

Blood sugar time curves, when obtained without simultaneously determined respiratory metabolism curves, yield limited, though useful, information. The only indications of a hyperglycemic response to dextrose are (a) that the dextrose ingested, or at least part of it, has been absorbed, and (b) the degree of hyperglycemia is some indication of tolerance, namely, an index of the disproportion between the rate at which dextrose is being absorbed from the alimentary canal and the rate at which it is being utilized. (By utilization is meant the combined mechanisms of oxidation and storage.) The respiratory metabolism is a quantitative index of oxidation.

There are many necessary precautions to be taken in order to be reasonably certain that the respiratory quotients obtained during these tests approximate true metabolic conditions. As is well known, the respiratory quotient at the mouth is not necessarily the respiratory quotient in the body tissues. There are many factors, technical, psychologic, etc., which influence quotients and make difficult their interpretation.

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7. Finley, F. G., and Rabinowitch, I. M.: Quart. J. Med. **17**:260, 1924.

The possible sources of error and details of the precautions necessary were previously discussed by me.[8] It is therefore unnecessary to repeat them here.

Respiratory exchange and blood sugar analyses were made before and thirty, sixty, one hundred and twenty and one hundred and fifty minutes after the oral administration of 100 Gm. of dextrose. For the calculation of grams of carbohydrate oxidized per hour, urinary nitrogen estimations were not made, because of the uncertainty that the urinary nitrogen obtained at the time of the test represents the protein metabolism of that period. Fifteen per cent of the total calories per hour were allowed for the protein metabolism.[9] The remaining calories, assumed to be derived from the carbohydrates and fats, were apportioned according to the Zuntz-Schumberg tables as modified by Williams, Riche and Lusk.[10] The results of such a study, including the blood sugar time curves obtained at the time of the test, are recorded in table 1.

TABLE 1.—*Respiratory Metabolism and Blood Sugar Time Curve Obtained Simultaneously Following Ingestion of Dextrose* *

	Respiratory Exchange, Liters per Hour		Respiratory Quotient		Calories		Grams of Carbo- hydrate Oxidized per Hour	Blood Sugar, per Cent
Period	Oxygen Consump- tion	Carbon Dioxide Produc- tion	Total	Non- protein†	Per Hour	Percentage Increase Above Basal		
Fasting.............	11.65	9.67	0.830	0.835	55.72	..	5.0	0.113
Given 100 Gm. of dextrose in 250 cc. of water flavored with lemon juice								
30 min. later.....	12.09	9.71	0.804	0.802	57.44	3	3.9	0.172
60 min. later.....	12.28	10.06	0.818	0.822	58.59	5	5.2	0.232
120 min. later.....	12.48	9.91	0.794	0.794	58.98	6	3.6	0.250
150 min. later.....	11.87	9.69	0.817	0.818	56.65	2	4.6	0.244

* The patient was a woman, aged 36.
† Calculated by allowing 15 per cent of the total heat production for protein metabolism.

It will be observed that there was a definite decrease in the rate of oxidation of carbohydrates, according to: (a) the respiratory exchange, (b) the grams of carbohydrates oxidized per hour and (c) the specific dynamic action of the ingested dextrose; there was no increase of the respiratory quotient, compared with the normal of 0.12, and the maximum increments of oxygen consumption and carbon dioxide and heat production were 4, 7.1 and 5.8 per cent, respectively, compared with the normal averages of about 12, 25 and 14 per cent. The maximum amount of sugar oxidized per hour was 5.2 Gm., compared with the normal of 10 Gm. or more.

In all, twenty cases were similarly investigated. Because of possible sources of error met with, namely, overventilation, apprehension, restlessness and cough, the results of only thirteen experiments were

8. Rabinowitch, I. M.: J. Clin. Investigation 2:143, 1925.
9. Voit, E.: Ztschr. f. Biol. 41:188, 1901.
10. Williams, H. B.: Riche, J. A., and Lusk, G.: J. Biol. Chem. 12:349, 1912.

regarded as satisfactory and comparable with the normal. A summary of the results is shown in table 2. The data appear to indicate defective carbohydrate metabolism in the group, as a whole, though the findings were normal in some cases. It must be observed, however, that the number of observations was small, and that there was a wide range between maximum and minimum values. This applies also to the standards with which the results were compared. It was therefore considered advisable to test the data still further by a more detailed statistical analysis.

In their "Food Ingestion and Energy Transformations," Benedict and Carpenter [11] recorded all of their results obtained in normal subjects. Because of the completeness of the necessary details, the data lend themselves readily to statistical treatment. Tables 126 to 135, inclusive,

TABLE 2.—*Minimum, Maximum and Average Increments Above Basal Level, Following Ingestion of 100 Gm. of Dextrose*

Subjects	Respiratory Quotient*			Carbon Dioxide Production†			Oxygen Consumption†			Heat Production†			Grains of Carbohydrate Oxidized per Hour
	Low	High	Average	Low	High	Average	Low	High	Average	Low	High	Average	
Normal....	0.07	0.18	0.126	12.3	35.0	24.5	2.9	21.3	11.9	6.1	24.2	14.0	10+
Average of all abnormal cases	0	0.18	0.095	4.0	27.2	16.8	3.5	17.8	8.3	5.8	16.5	9.8	

* Total increase above basal.
† Percentage increase above basal.

afford determination of the maximum increments of the respiratory quotients, oxygen consumption, carbon dioxide production and heat production observed in each experiment. Arithmetical means, standard deviations and probable errors of means were, therefore, readily calculated. Our own data were treated similarly. The combined results are shown in table 3 and are summarized in table 4.

From the ratios of the differences between the means to the probable errors of the differences (table 4), it is concluded that it is highly probable that the differences noted between the normal and our cases in this study were not due to chance alone. Conservative statistical practice, in interpreting differences between means, requires that a difference should be at least four times its probable error before one can assume certainty. The probability, however, that the differences noted between the normal and the abnormal cases were not due to chance alone is increased by the findings with the blood sugar time curves. The results of diet and insulin therapy appear to indicate a causal, rather than an accidental, association between defective carbohydrate metabolism and delayed healing of wounds.

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11. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations, Washington, D. C., Carnegie Institution. 1918, publ. 261.

TABLE 3.—*Statistical Analysis of Data on Respiratory Exchange Obtained in Normal and Abnormal Subjects Following Ingestion of 100 Gm. of Dextrose*

Normal

Subject	Respiratory Quotient × 100 Basal (b)	Maximum (m)	Increase (m—b)	Oxygen Consumption, Cc. per Min. Basal (b)	Maximum (m)	Increase $\frac{m}{b} \times 100$	Carbon Dioxide Production, Cc. per Min. Basal (b)	Maximum (m)	Increase $\frac{m}{b} \times 100$	Heat Production, Calories per Min. Basal (b)	Maximum (m)	Increase $\frac{m}{b} \times 100$
K.H.A.	84	101	17	226	240	107.6	187	235	125.6	1.08	1.21	112.4
J.C.O.	74	81	7	252	272	107.9	187	210	112.3	1.19	1.28	107.6
J.C.C.	79	94	15	232	272	117.2	184	242	131.5	1.11	1.33	119.8
L.E.E.	78	96	18	236	255	108.0	183	237	129.5	1.13	1.26	111.5
C.H.H.	87	94	7	193	231	119.7	167	203	121.6	0.94	1.12	119.1
H.L.H.	82	98	16	224	256	114.3	183	230	125.7	1.08	1.24	114.8
P.F.J.	84	99	15	238	245	102.9	200	239	119.5	1.15	1.22	106.1
B.M.K.	70	79	9	217	243	112.0	152	188	123.7	1.02	1.16	113.7
A.J.O.	87	96	9	253	308	121.3	220	297	135.0	1.24	1.54	124.2
Dr.P.R.	78	91	13	186	202	108.6	146	177	121.2	0.89	0.99	111.2
Arithmetical mean			12.6			111.9			124.5			114.0
Standard deviation			4.2			6.02			5.6			5.6
Probable error of mean			0.92			1.30			1.22			1.22

Abnormal

Subject	Respiratory Quotient × 100 Basal (b)	Maximum (m)	Increase (m—b)	Oxygen Production, Liters per Hour Basal (b)	Maximum (m)	Increase $\frac{m}{b} \times 100$	Carbon Dioxide Production, Liters per Hour Basal (b)	Maximum (m)	Increase $\frac{m}{b} \times 100$	Heat Production, Calories per Hour Basal (b)	Maximum (m)	Increase $\frac{m}{b} \times 100$
4699/31	83	83	0	11.65	12.48	107.1	9.67	10.06	104.0	55.72	58.98	105.8
2975/31	86	94	8	9.40	10.34	110.0	8.09	9.74	120.4	45.33	50.95	112.4
4381/31	79	91	12	11.77	12.43	105.6	9.25	11.20	121.1	55.67	60.47	108.6
4006/31	81	91	10	11.20	11.91	106.3	9.12	10.90	119.5	53.33	58.17	109.1
4445/31	79	84	5	11.32	11.91	105.2	9.00	10.02	111.3	53.67	57.19	106.5
5326/31	80	88	8	12.57	14.35	114.1	10.02	12.38	123.5	59.58	68.15	114.4
5373/31	78	83	5	14.63	15.15	103.5	11.45	12.66	110.6	69.23	72.59	104.9
53/32	74	92	18	12.06	13.27	110.0	8.91	11.34	127.2	56.45	63.84	113.1
714/32	76	90	14	12.68	13.48	106.3	9.68	11.61	119.9	59.56	64.05	107.5
960/32	85	94	9	13.80	16.23	117.8	11.72	13.26	113.1	66.42	77.41	116.5
592/32	80	95	15	11.28	11.76	104.2	9.04	10.30	113.9	53.59	56.43	105.8
760/32	77	90	13	9.84	11.16	113.2	7.55	9.58	126.4	46.33	53.36	115.1
906/32	80	87	7	11.44	13.48	108.3	9.91	11.68	117.6	59.00	64.09	108.6
Arithmetical mean			9.5			108.3			116.8			109.8
Standard deviation			4.0			4.1			6.8			4.0
Probable error of mean			0.75			0.77			1.27			0.75

TABLE 4.—*Summary of Statistical Analysis of Data on Respiratory Exchange Obtained in Normal and Abnormal Subjects Following Ingestion of 100 Gm. of Dextrose*

Phenomenon	Subject	Arithmetical Mean (a)	Standard Deviation (b)	Probable Error of Mean (c)	Difference Between Means (d)	Probable Error of Difference (e)	d/e
Respiratory quotient*	Normal	12.6	4.2	0.92 }	3.1	1.19	2.6
	Abnormal	9.5	4.0	0.75			
Oxygen consumption†	Normal	111.9	6.02	1.30 }	3.6	1.51	2.4
	Abnormal	108.3	4.1	0.77			
Carbon dioxide production†	Normal	124.5	5.6	1.22 }	7.7	1.76	4.3
	Abnormal	116.8	6.8	1.27			
Heat production†	Normal	114.0	5.6	1.22 }	4.2	1.43	2.9
	Abnormal	109.8	4.0	0.75			

* Total increment × 100.
† Percentage increment.

COMMENT ON RESULTS

The usual conditions that might explain impaired healing of tissue appear to have been excluded (syphilis, etc.). All conditions which tend to disturb carbohydrate metabolism and which may lead to blood sugar time curves similar to those observed in these cases were also excluded (nephritis, hyperthyroidism, etc.). How are these data, therefore, to be explained? Infection was present in some of the cases. Infection is known to lead to disturbed carbohydrate metabolism in the nondiabetic as well as in the diabetic patient, and Richardson and Levine,[12] in a study of respiratory metabolism in infection, observed that though there was no direct evidence of a defect in the capacity to oxidize carbohydrates in infection, a defect was inferred from the data. Infection, however, does not explain the picture entirely, since many patients showed no infection, at least not according to the usual indications (local condition, fever, leukocytosis, etc.).

Are these subjects diabetic? The blood sugar time curves, respiratory quotients, rates of oxidation of carbohydrates and specific dynamic responses to the ingestion of dextrose differ in no way from those found in diabetes. In the absence of glycosuria, however, one hesitates to place them in this category. Joslin,[13] when advised of our experiences, also stated that he would hesitate to put these patients in the regular group of diabetic patients, though the fasting blood sugars may have reached 0.14 or 0.5 per cent. Langdon Brown,[14] on the other hand, stated quite recently that he is almost prepared to assert that every one with resting hyperglycemia has diabetes. Because of our search for these cases and routine studies, the number is increasing. For this reason, I further hesitate to classify these patients as diabetic, since this would tend to alter the values of mortalities and morbidities and our data would no more be comparable with other clinics for diabetes, and comparable data are essential for proper statistical studies. As stated, the first patient, after having been observed for approximately seven years, proved not to have diabetes. On the other hand, the following experience was met with recently.

REPORT OF CASE

A woman, aged 52, was admitted to the gynecologic service of the Montreal General Hospital on Dec. 24, 1931, for a hysterectomy. Following this operation, the abdominal wound failed to heal at the usually expected rate. There were no signs or symptoms to suggest diabetes, and at no time was there any glycosuria. The blood sugar time curve, however, revealed a marked disturbance of carbohydrate metabolism. Following the institution of dietetic and insulin treatment, the wound healed, and the patient was discharged from the hospital on Jan. 10, 1932. Shortly after discharge, however, both dietetic and insulin treatment were discontinued and the wound broke down. She was read-

12. Richardson, H. B., and Levine, S. Z.: J. Biol. Chem. **63**:465, 1925.
13. Joslin: Personal communication to the author.
14. Brown, W. L.: Post-Grad. M. J. **8**:49, 1932.

mitted on January 25. There was a history of respiratory infection for some days prior to admission, and shortly after admission the signs and symptoms of pneumonia developed.

The interesting finding in this case is that with the onset of the pneumonia, glycosuria appeared and was accompanied by marked hyperglycemia; the blood sugar was 0.400 per cent, and during the febrile course of the disease the patient required 60 units of insulin a day to keep the blood sugar under control. Is it possible, therefore, that many of these people have diabetes; that glycosuria is not observed because the blood sugars are below the renal threshold for dextrose, and that the disease becomes obvious only when these persons are exposed to some injury or infection which causes further loss of carbohydrate tolerance? Because of this possibility, all of these people are, as a routine measure, being referred to our diabetic clinic to be observed at three month intervals. Experiences during the next five years with these cases should clarify the picture. The purpose of this communication was to draw attention to the association between defective carbohydrate metabolism and delayed healing and to the results which may be obtained with a diet and insulin therapy.

ADDENDUM

Since this paper was submitted for publication, the findings of Williams and Dick on the relationship between dextrose tolerance and infection have been published,[15] and, though the problem was approached from a different point of view, the findings are essentially the same as our own. Acute infectious diseases were studied, and it was observed that these may be accompanied by an increase in the height of the blood sugar concentration during fasting and by alteration in the blood sugar curves following the ingestion of dextrose. This applied both to animals and to man. The loss of carbohydrate tolerance may last for some time—weeks or months—and can be improved by the administration of insulin. The authors suggest that in infectious diseases there are often an injury of the islands of Langerhans and the production of a condition somewhat analogous to diabetes; and recovery of carbohydrate tolerance following insulin is explained by immunity to the infecting organism and by regeneration of the islands of Langerhans.

15. Williams, J. L., and Dick, G. P.: Decreased Dextrose Tolerance in Acute Infectious Diseases, Arch. Int. Med. **50**:801 (Dec.), 1932.

RESULTS OF SURGICAL TREATMENT OF MALIGNANT GOITER

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The results of treatment of malignant conditions affecting the thyroid may be far better than certain writers would lead one to believe. Moreover, the situation is not hopeless even when the growth has involved surrounding tissues or extended to lymphatic glands. I reported extensive involvement of surrounding tissues in a woman ten years ago; yet she lived over sixteen years following operation and died from apoplexy at the age of 73.[1] This case and two others in which there was secondary involvement of the lymphatic glands of the neck were reported later, and one of the patients is still living and well eleven years following operation; the other lived nine years and was lost from observation. The outlook is encouraging in many of these cases because adenocarcinoma, the most common malignant condition affecting the thyroid, is slow in development; it metastasizes late and is radiosensitive. These facts have been confirmed by the reports of many other recent observers.

Permanent results are influenced to a considerable extent by the same factors which favor satisfactory results in most malignant conditions: location, extent, duration of the disease and type of malignancy, and the skill, experience and methods of the operating surgeon. Of greatest importance, influencing operative results, I believe to be the use of radium and x-rays in combination with electrosurgery.

LOCATION

Growths located in the isthmus or the anterior surface of the gland, relatively distant from the main lymphatics and blood vessels, do not tend to metastasize as early as those deeply located directly over the great vessel and lymphatic trunks. Such location also makes infiltration of important surrounding structures less likely and complete surgical removal more readily possible.

Duration is frequently difficult to determine. Many patients are incredibly unobservant about the development of growths, even in exposed and readily accessible locations. It is obvious that the longer

1. (a) Tinker, M. B.: The Desperate Risk Goiter, J. A. M. A. **79:**1291 (Oct. 14) 1922; (b) End-Results of Treatment in Certain Forms of Malignancy of the Neck, Ann. Surg. **76:**335 (Sept.) 1922; (c) Tr. Am. S. A. **40:**10, 1922.

the disease has existed the greater the likelihood of metastasis and involvement of surrounding tissues and consequent difficulty in removal. The well recognized slow growth of some of these malignant conditions is a decidedly favorable factor. Kocher [2] reported a case existing ten years without metastasis. The known duration of life was fifteen years in a patient coming under my care twelve years following operation in another clinic; when first seen by me the involvement was evidently too extensive for further surgical procedures; yet after radium treatment this patient lived three years longer in relative comfort.

Small growths, particularly encapsulated growths, which have not broken through and malignant areas discovered only by pathologic examination after operation, located within an enlargement apparently benign, are usually favorable. As noted before, large, extensive growths do not preclude many years of comfortable life and a death from other causes. Extension to the neighboring lymphatic glands of the neck is also not necessarily fatal, although such extension would undoubtedly increase the gravity of the situation. Metastatic extensions to distant parts of the body have proved fatal thus far in my experience, although considering the character of some of these growths this would not seem inevitable.

TYPE OF MALIGNANCY

It has long been known that certain goiters, which both clinically and pathologically are apparently benign, may metastasize and cause the death of the patient. Metastasis is most likely to occur in the flat bones. This was first noted by Cohnheim [3] fifty-six years ago. In a most thorough recent discussion of this subject, Barthels [4] quoted eighty-six writers who have reported one or more such cases. The diagnosis was confirmed by microscopic examination in forty-five cases. A postmortem examination was made in about one third of the cases. Most of the additional cases have shown all the clinical characteristics of a malignant condition, and in some of them there has been a relatively satisfactory pathologic examination. There would seem to be no possible question as to the malignant characteristics of these microscopically benign growths. Two such cases have come under my care; in one the patient died of metastasis to the spine, and in the other of intra-abdominal metastasis.

The adenocarcinomas have been found by all observers the most favorable for treatment. Excellent results have also been obtained in many cases of papillary carcinoma. The infiltrating scirrhous car-

2. Kocher, Theodor: Deutsche Ztschr. f. Chir. **91**:197, 1908.

3. Cohnheim: Virchows Arch. f. path. Anat. **48**:547, 1876.

4. Barthels, C.: Ergebn. d. Chir. u. Orthop. **24**:162, 1931.

cinomas and sarcomas have been found hopeless by practically all observers. Even this view may have to be changed. Gottstein [5] has reported a five year cure in a case diagnosed as round cell sarcoma by Professor Winkler of Breslau.

CHARACTER OF TREATMENT

Surgical measures alone have given freedom from symptoms over long periods of time with apparent cure in a few cases. Irradiation alone has given fewer apparent cures in another group of cases. A combination of operation and irradiation has given favorable results in a considerably larger number of cases than operation or irradiation alone. Electrosurgery has not been used for a long enough time to show what permanent results may be expected, but the fact that the electric current seals blood vessels and lymphatics certainly indicates that metastasis will be prevented in most cases. The destruction of malignant cells by the current should also give a better prospect of satisfactory results. A number of writers have pointed out that biopsy or any manipulation may readily dislodge cells of malignant adenoma and cause their dissemination. The use of electrosurgery and gentleness in manipulation seem to me largely to eliminate this risk. Cuts made from photographs and photomicrographs in previous articles [6] show exactly what may be attained in clotting vessels and surface coagulation. In view of these and many other advantages, it seems surprising that so few surgeons are using electrosurgery. Irradiation alone, whether by x-rays or by radium, has not given permanent cure in any of my cases to this date. It is only fair to state that irradiation alone has been used in only those of my cases in which the growth was so located or so extensive that any form of surgical intervention seemed contra-indicated. Operation alone has given a four year cure in only one of my cases. Extensive radical operations with excision of the carotid arteries, jugular vein and the vagus nerve by Theodor Kocher and a number of earlier operators were followed with operative recovery, but do not seem to offer any advantage so far as permanent results are concerned. I have removed a large part of extensive growths infiltrating the great blood vessel sheath and the trachea and larynx in five cases. A sufficient amount of tissue was left surrounding the blood vessels to make reasonably certain that rupture of the vessels would not occur. The microscopic pathologic examinations have been confirmed by well known pathologists. The use of radium following these incomplete

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5. Gottstein: Ber. d. Breslauer chir. Gesellsch., Jan. 20, 1932.

6. Tinker, M. B.: Surg., Gynec. & Obst. **52**:508 (Feb. 7, no. 2 A) 1931; Ann. Surg. **94**:587 (Oct.) 1931.

operations has apparently controlled the further extension of the growth and apparently resulted in a cure in three cases. This experience has still further confirmed my belief that more radical operation is not justified. It is evident that gentle handling of the tissue tends to prevent loosening of cancer cells and metastasis; also that tissues sustaining minimum damage from handling would have a better prospect of healing. As thorough eradication of the growth as is possible seems somewhat to increase the prospect of a satisfactory result though irradiation takes care of extensive involvement in many cases if the great bulk of malignant growth is removed. The advantages of electrosurgery seem so apparent that I believe that it should certainly be used in all operations for malignant conditions, even if the surgeon does not choose to use it in all of his operations on the thyroid.

PROGNOSIS

Pessimistic prognoses vary from those of Hertzler [7] and Jackson,[8] who question whether any patient with a real malignant growth of any extent ever recovers, to those of Crile,[9] Rienhoff,[10] Toland and Kroger [11] and Crotti,[12] who believe that when extension through the capsule has occurred operation is useless. Some of these writers advise irradiation without operation; some advise irradiation if there is a pathologic diagnosis of a malignant condition after operation; some advise operation in early cases, and some offer no suggestions as to treatment.

The more optimistic point of view combines operation and irradiation. The number of recent writers who take a more optimistic view as to the possible results in malignant goiter is considerable. For over seventeen years, due largely to the suggestions and encouragement of Dr. Howard A. Kelly of Baltimore, I have been using irradiation in conjunction with surgical intervention. Emboldened by the fact that two of my patients were living over seven years after operation, I made a brief report on the combined methods in 1922.[1a] In 1928, the number of my cases had increased [1b, c] with four patients living five or more

7. Hertzler, A. E.: Diseases of the Thyroid Gland, St. Louis, C. V. Mosby Company, 1922, p. 131.

8. Jackson, A. S.: Goiter and Other Disease of the Thyroid, New York, Paul B. Hoeber, Inc., 1926, p. 156.

9. Crile, in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1928, vol. 2, p. 725.

10. Rienhoff, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1929, vol. 6, chap. 1, p. 225.

11. Toland, C. G., and Krager, W. P.: S. Clin. North America **10**:1201 (Oct.) 1930.

12. Crotti, André: Thyroid and Thymus, Philadelphia, Lea & Febiger, 1918, p. 179.

years after combined treatment, three for six years or over, and one for fourteen years; one patient lived for nine years, dying from unknown causes. Since this report a patient, aged 73, has died of apoplexy over sixteen years after operation. In 1927, Bowing [13] reported results from combined treatment at the Mayo Clinic. The same year Portmann [14] compared surgical measures alone, with 9 per cent five year cures; irradiation alone, with no five year cures, and combined treatment, with 22.6 per cent five year cures, at Crile's clinic. In 1928, Pemberton [15] reported with much thoroughness a large series of cases, stating in conclusion that the results of surgical treatment of carcinoma of the thyroid are more encouraging than is popularly believed. He reported 32 per cent of the patients in whom malignant disease was diagnosed before operation as living three years or longer, and stated that probably in no other malignant disease are x-rays and radium so valuable. Operation in conjunction with irradiation has been employed in the Mayo Clinic since 1918. Barthels [16] reported patients free from symptoms for twenty-four, twelve, eleven and six years. The results of irradiation alone are less certainly good. Barthels also advocates exploratory excision for diagnosis, and if sarcoma or carcinoma is found by biopsy, discontinuance of the operation and irradiation are advised. On the other hand, when one deals with malignant papilloma or adenocarcinoma, further operation is justified. Thirty-three per cent of his patients are living over four years following biopsy. Strauss [17] advocates radical excision, including the lymphatic glands, which he finds affected in about one half of his cases. He considers radical operation and postoperative roentgen treatment the method of choice. Ward and Carr [18] reported 14 per cent of patients living without recurrence in cases from Terry's clinic in San Francisco in which there had been a diagnosis of cancer before operation, formerly considered a discouraging group of cases. Holfelder [19] reported 55.5 per cent of his patients free from symptoms after five years by combined operation and irradiation. Bucky,[20] speaking from the standpoint of the radiologist, has recently advocated the combination of electrosurgery and irradiation in treating

13. Bowing, H. H.: Am. J. Roentgenol. **18**:501 (Dec.) 1927.

14. Portmann, U. V.: Radiation Therapy in Malignant Disease of the Thyroid Gland, J. A. M. A. **89**:1131 (Oct. 1) 1927.

15. Pemberton, J. de J.: Ann. Surg. **87**:369, 1928.

16. Barthels, C.: Beitr. z. klin. Chir. **142**:711, 1928.

17. Strauss, L.: Beitr. z. klin. Chir. **148**:40, 1929.

18. Ward, Robertson, and Carr, J. L.: Tr. Am. A. Study Goiter, 1930.

19. Holfelder, H.: Zentralbl. f. Chir. **58**:940 (April 11) 1931.

20. Bucky: Zentralbl. f. Chir. **59**:1393, 1932.

a number of malignant conditions hitherto considered hopeless. There is a difference of opinion as to biopsy. Clute [21] reported fatal pneumonia following biopsy, and expressed the belief that the rate of growth of the tumor is distinctly accelerated. On page 7 of this same article he expressed his belief that "it is never justifiable to incise a potentially malignant adenomatous nodule for biopsy because of the ease with which these tumors gain access to the blood stream." If radio cutting were used, this danger would almost certainly be avoided, by reason of the fact that the current, particularly the medium or slow cutting current, almost certainly seals blood vessels and lymphatics.

PERSONAL RESULTS OF OPERATION AND IRRADIATION

Among the patients operated on and treated by irradiation, the following number of patients were living and symptom-free for the designated period of years: ten for three years, nine for four years, eight for five years, six for six years, five for seven years, two for eleven years and one for thirteen years. One patient died from an unknown cause after nine years and one died from apoplexy at 73 years of age after sixteen years.

Of those with early extension or recurrences, eight died from two months to two and one-half years following operation. These patients were evidently in serious condition with advanced malignant growths, but were given the benefit of the doubt. Four others in apparently equally bad condition have recovered and remained well for several years. Operation has been refused in only five cases. One of these patients with a large apparently adenomatous goiter had complete consolidation of the left lung which was apparently a solid malignant mass, as shown by roentgen examination. One patient died ten days after leaving the hospital, evidently in too serious condition to be benefited by any treatment whatever. In another case the growth was so extensive and firmly fixed, after thirteen years' duration, that operation was evidently contraindicated. Another man with cerebral symptoms had a low fever for six weeks, the cause of which was undetermined by internists. Finally, one patient refused operation.

There were ten cases reported as suggestive of malignant conditions, or in some instances diagnosed as malignant by one pathologist and as doubtful by others. The microscopic slides will be referred to other competent pathologists as soon as convenient. All of these patients are living and apparently well.

21. Clute, H. M., and Smith, L. W.: Cancer of the Thyroid Gland, Arch. Surg. **18**:18 (Jan.) 1929.

CONCLUSION

In conclusion, I should like especially to emphasize three points:

1. Exceptionally favorable results with slow growing, late metastasizing, radiation-sensitive growths which make up a large proportion of the total malignant growths of the thyroid. If untreated these go on inevitably to a fatal outcome.

2. The value of combined treatment by irradiation and surgical measures, which in the hands of many surgeons in widely separated locations has given a high percentage of cures or at least relatively comfortable life for many years.

3. The great promise of electrosurgery which, by destruction of cancer cells, leaving nonabsorbing surfaces and sealing the vessels and lymphatics, should reduce the likelihood of local recurrence and prevent metastasis.

A REVIEW OF UROLOGIC SURGERY

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URETER

Surgery.—Marion [28] reviewed his ideas on the technic of total ureteronephrectomy. He does not use the large lumbo-abdominal incision. To perform complete nephro-ureterectomy, a lumbar incision and a low abdominal incision are necessary. He employs the lateral vesical route to reach the pelvic ureter, pushing the peritoneum aside, loosening the bladder from the pelvis and approaching the ureter at the level of the vesical wall. A definite procedure cannot always be determined before operation. In some cases the condition is definite and the plan can be outlined before operation, particularly in cases such as those of ureteropyonephrosis. In other cases the necessity for removing the ureter may not be ascertained until the kidney has been examined. Marion expressed the belief that in these cases the most simple procedure is to approach the ureter by the latero-iliac route, somewhat high up, and free the ureter down to the bladder. He also considered secondary ureterectomy that is necessary on account of the condition of the bladder, as in tuberculous or malignant stump of the ureter.

[COMPILERS' NOTE.—Since the arrival of the urographic era an accurate preoperative diagnosis usually has been made, and the technic of

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28. Marion, G.: A propos de la néphro-urétérectomie, Bull. et mém. Soc. nat. de chir. **58**:602 (April 30) 1932.

combined ureteronephrectomy has been greatly simplified. The surgeon can outline the procedure of the operation instead of using the traumatizing, large, lumbo-abdominal incision of the past. Marion, Beer, Papin, Gutierrez and others have emphasized the fact that when the pathologic processes of the kidney have involved the ureter, or vice versa, the proper indication is usually to perform ureteronephrectomy by means of two separate incisions, in an effort to remove in a single piece the diseased ureter and kidney; this obviates the further difficulties arising from a ureteral stump left behind at the time of nephrectomy.]

Scholl [29] stated that stricture with obstruction of the ureter is commonly found associated with renal tuberculosis, and partial or complete ureterectomy occasionally has been advocated. The majority of the reports in which removal of the tuberculous ureter was advised were based on reviews of nephrectomy done in the early decades of urologic surgery. Accurate methods of urologic diagnosis, early recognition of the condition present and skilful, rapid technic, giving special attention to the ureteral stump, have reduced the complications frequently occurring in earlier cases and have lessened the indications for ureterectomy. In a review of 1,023 cases of nephrectomy for tuberculosis, Israel stated that the method of treating the ureter has no marked influence on closure of the wound.

With regard to nontuberculous disease, it is generally agreed that the ureter should be completely removed with the kidney in cases of papillary epithelioma of the renal pelvis; an extension or transplant to the ureter occurs in the majority of cases. Each case of nontuberculous, dilated, infected ureter, associated with stones or pyonephrosis, must be treated individually as the condition demands and as the state of the patient permits. The need later for nephro-ureterectomy or ureterectomy arises in only a small percentage of cases. In a report of 475 cases of hydronephrosis and 471 cases of pyonephrosis in which nephrectomy was performed, complete nephro-ureterectomy was done in only 18 of the cases of hydronephrosis. In none of the remaining cases were operations needed on the remaining ureter after nephrectomy. In only 3 of the 471 cases of pyonephrosis was nephro-ureterectomy found necessary and performed.

In most cases, even when the ureter is extremely dilated, it is not necessary to remove it simultaneously with the kidney. In cases in which the ureter and any retained contents are infected and obstruction to the lower part of the ureter occurs, this obstruction must be relieved. If it is impossible to relieve the obstruction by conservative methods, primary nephro-ureterectomy or secondary ureterectomy should be performed.

29. Scholl, A. J.: The Ureter After Nephrectomy. West. J. Surg. **40**:279 (June) 1932.

Four cases of pathologic changes in the ureter after nephrectomy were reported. Various procedures were done in these cases, such as ureterectomy, cauterization and sterilization of the ureteral contents.

[COMPILERS' NOTE.—Simple nephrectomy is sufficient in the treatment of the majority of patients with renal tuberculosis in whom the lesion is confined to the kidney. On the other hand, there are two types of tuberculous lesions in which both the kidney and ureter are involved; in these cases total ureteronephrectomy is usually indicated in order to avoid the common complications of lumbar fistula or incurable tuberculous cystitis. These two types of lesions are readily visualized in a ureterogram. They are the rosary type of tuberculous ureter, in which the ureter is manifestly infiltrated with tuberculous caseous material, and the megalo-ureter, in which there is enormous dilatation of the ureter or definite tuberculous ureteritis and periureteritis.

The part that the ureter plays following nephrectomy presents a problem of significance in modern urology, particularly on account of the many complications that may arise, and because, as was pointed out before, the lesions of the ureter must be treated individually as the condition demands and as the state of the patient permits. If palliative cystoscopic measures do not relieve the pathologic condition, it is evident that the ureteral stump must be regarded as potentially presenting a surgical condition.]

Walters [30] stated that transplantation of the ureters to the sigmoid-colon has been done at the Mayo Clinic since 1912 in the treatment of exstrophy of the bladder and other vesical and urethral abnormalities in which the bladder failed to hold urine. The method used consists of transperitoneal transplantation of the ureters to the sigmoid-colon in separate stages, with an interval of from twelve to fourteen days between operations. The original method of submucosal transplantation reported by Coffey as applying to experimentally transplanted common bile ducts in animals was used. The transplantations were done without the use of tubes or catheters. Eighty-four patients with exstrophy of the bladder, including those with complete epispadias, have been treated at the clinic in this manner. Within the last seven years Walters has operated in 20 of these cases, in 16 for exstrophy of the bladder, in 2 for complete epispadias and in 2 for congenitally deformed or traumatized urethras with total urinary incontinence. One death occurred among the 20 cases.

30. Walters, Waltman: Transplantation of the Ureters to the Sigmoid-Colon for Exstrophy of the Bladder and Other Ureteral Abnormalities with Urinary Incontinence (Unilateral Versus Simultaneous Bilateral Transplantation), Proc. Staff Meet., Mayo Clin. 7:470 (Aug. 10) 1932.

Experience at the clinic has shown that it is unnecessary to use either tubes or catheters in transplantation of the ureters to the sigmoid-colon if one normal sized ureter is transplanted at a time. In the treatment of exstrophy of the bladder and other congenital abnormalities of the bladder and urethra, with total incontinence, the risk of such operation is far less for young children than that of simultaneous bilateral ureteral transplantation.

Ureteral Reflux.—Lepoutre [31] reported a case of congenital dilatation of the urinary tract in a girl, 10 years of age. She had had unexplained attacks of fever from infancy and pus in the urine. At cystoscopy 500 cc. of residual urine was found, which was difficult to clear of pus. The meatus of the left ureter was dilated; it had a circular orifice, resembling the entrance of a diverticulum; from time to time a wave of contraction passed over it. On the right side, the meatus, which was oblique and of an oval shape, was too wide, and contracted at regular intervals. Cystoroentgenography with collargol showed a reflux and enormous dilatation of the left ureter and pelvis. The bladder was deformed on the right side, and had the appearance of a diverticulum. Because of the rather delicate condition of the patient, only palliative treatment was given. Occasional lavage with collargol clears the urine and prevents febrile attacks. The prognosis in such a case is not favorable, and the patient probably cannot meet the demands of maternity.

Chronic pyuria in a child, as in an adult, requires complete urologic examination. Significant symptoms are lumbar pain at the time there is urgency, and chronic retention. This type of dilatation may involve an isolated portion of the urinary tract, causing megalo-ureter and megalopelvis. In this case it attacked the calices, pelvis and ureteral meatus at the same time, causing reflux. The malformation may not cause any apparent trouble for a number of years until some complication, generally an infection, makes it evident.

[COMPILERS' NOTE.—The subject of congenital malformation of the upper part of the urinary tract has been considered recently by Campbell, who has reported unusual cases of this type from the Bellevue Clinic and the Babies' Hospital of New York. It is well known that the so-called pyelitis of childhood, which does not respond to medical treatment, must be considered as the result of congenital malformation of the upper part of the urinary tract. Every newly born child with abdominal pain or urinary symptoms should have a complete urologic examination, including a cystogram. In this particular type of lesion of vesicorenal reflux, when a "golf hole" type of ureteral orifice is

31. Lepoutre, C.: Dilatation de l'arbre urinaire et reflux vésico-urétéral d'origine congénitale, Bull. Soc. franç. d'urol., May 9, 1932, p. 185.

present, and the lesion is characterized by hydro-ureter and hydro-nephrosis in which the kidney as a rule is practically functionless, the proper indication is usually ureteronephrectomy.]

Tumor.—Fowler [32] reported a case of solitary papilloma of the lower part of the right ureter occurring in a man, aged 42. He had had intermittent hematuria for twenty-five years. The attack before the patient came under observation had lasted continuously for a month. Cystoscopy revealed a large papillomatous growth on the right side of the bladder, close to the vesical outlet. At operation a large tumor was found attached by a narrow pedicle to the right side of the base of the bladder. Numerous small papillomas were clustered about the urethral orifice. These were all cauterized. Thirty-two months later cystoscopy showed the presence of 4 small papillomas, about 1 cm. in diameter, on the anterior wall of the bladder near the vertex and a similar growth on the left lateral wall. At that time treatment was not acceptable, and several years later examination revealed an extensive growth involving the anterior wall and filling the vertex of the bladder. The whole tumor-bearing area was widely resected in one piece. This included the area of normal vesical wall between the separate growths.

The patient had several attacks of hematuria during the next few years, and finally died suddenly. At necropsy the right ureter was dilated to a diameter of 1.5 cm. within 2.5 cm. of the bladder. At this point there was a papillomatous tumor, the base of which was 1 cm. and the villous mass 2 cm. long, projecting into the lumen of the dilated ureter. In the bladder just below the orifice of the left ureter was found another papillomatous mass with a base of 1.5 cm. Just above the urethral orifice were several minute papillomas.

Several interesting points in this case were emphasized. There was a definite history of intermittent hematuria over a period of twenty-five years prior to the patient's coming under observation. The longest period noted in reported cases has been fourteen years. The low grade of malignancy of the growth in the bladder was shown both clinically and histologically, placing it with the so-called benign papilloma group of tumors. The actual involvement of the bladder existed for more than the eleven years that this patient was under observation, as shown by the presence of a large tumor at the first examination and by the long history of hematuria. During this time the character of the growth did not change; it showed no tendency to undergo malignant degeneration. The original tumor had the clinical characteristics of papilloma. Recurrences took place in various parts of the bladder, not at the site of the original growth. The histologic examination of the tumor found

32. Fowler, H. A.: Solitary Papilloma of the Lower Ureter (Right) Secondary to Recurrent Papillomata of the Bladder, J. Urol. 27:561 (May) 1932.

at necropsy disclosed the type of cellular structure usually seen in papilloma. This observation appears to confirm the view that the type or character of cell in these papillary tumors does not change. If the original tumor is benign, any recurrence that may develop will have the same characteristic.

Mycosis Ureteritis.—Leinati [33] observed a case in which a ureter was the site of primary mycotic ureteritis following the experimental injection of a culture of Aspergillus fumigatus into the spleen of a rabbit. The fungus had not invaded any other region. The spores apparently did not find suitable ground for their development in the spleen, and in passing through the blood stream must have been either destroyed or eliminated through the renal filter without doing any injury until they entered the left ureter. At necropsy, eight days after the injection which caused death, not only was the aspergillosis present in the left ureter, but also dilatation. This dilatation evidently had existed previous to the mycotic infection, as the thickening of the wall of the ureter, especially the muscular hypertrophy, could not have developed in eight days. There was no mechanical obstruction of the ureter, nor was there any inflammatory stenosis caused by advanced ureteritis. The thickening of the wall and the muscular hyperplasia continued down to the bladder, the wall of which was indurated, with hyperplasia of the muscular tunics. The papilla of the ureter was conserved, and the right half of the bladder, with its ureter, presented no changes. It was therefore assumed that the ureterectasia was a primary congenital dilatation, dependent on obstacles of a functional nature or on lesions of the peripheral reno-ureteral nervous system.

The fact that the induration involved the entire urinary tract on the left side indicated that the cause had not been sufficient to diminish appreciably the functional activity of the excretory passages because of the compensatory hypertrophy that had developed. The kidney did not reveal lesions resulting from urinary stasis or from old inflammation, but only those related to aspergillar pyo-ureteronephrosis.

The ureterectasia was undoubtedly the effective cause of the grafting of the aspergillar infection on the ureter. In view of the experimental demonstration of the resistance of healthy urinary passages to infections, primary localization of infection in the urinary excretory passages can occur only when there is an anatomic or functional lesion. The urinary stasis in this case, although moderate, was sufficient to permit the growth and development of the aspergillar infection. As the inflammation spread to the entire wall of the lower third of the ureter, the attacks of acute retention began, leading at length to incoordination

33. Leinati, Fausto: Sopra un caso di ureteropionefrosi aspergillare sperimentale in progressa ureterectasia. Arch. ital. di urol. 8:55, 1931.

of movements and to spasms, finally resulting in dilatation of the pelvis, compression of the renal parenchyma and disappearance of the papillae. As the stasis and retention increased, the juxtavesical portion of the ureter gave way, and funnel-form dilatation of the lumen was produced. Thus was formed pyo-ureteronephrosis in which Aspergillus fumigatus could develop so well that histologic examination revealed even stages of fructification.

BLADDER

Tumor.—Gunsett [34] reported the cases of 26 patients with carcinoma of the bladder treated by him during seven years. Roentgen therapy was given in divided doses for about three weeks. Only the first patient was treated by means of a single application, 128 per cent of the erythema dose, but distributed over five days. In some of the cases this procedure was preceded or followed by electrocoagulation. Of the 26 patients, 10 are alive and free from symptoms: 1 patient ten years, 1 nine years, 2 eight years, 2 seven years, 1 six years, 1 four years and 1 three years following treatment. Eight (42 per cent) of 19 patients have remained well five years after observation.

Gunsett expressed the opinion that extensive tumors of the bladder should first be treated with deep roentgen rays; electrocoagulation should be employed as a means of destroying any portions of the growth which remain after the first type of treatment. In certain cases roentgen therapy may be used after electrocoagulation which has given imperfect results.

Lazarus and Rosenthal [35] stated that myxosarcoma of the bladder is rare and primarily a disease of early life. Diagnosis is possible only from a histologic study of the tumor, although the finding of small gelatinous-like bodies in the bladder is suggestive of tumor of this type.

Surgical excision does not give satisfactory results because of the prompt recurrence of the growth. Roentgen therapy has an appreciable effect on the neoplasm, as shown from the pathologic report of the authors' case. Coley's serum was found to be of no benefit. Total cystectomy offers the best possibility of cure in these cases.

Diverticulum.—Walters and Mulholland [36] reported a detailed study of 30 cases of diverticula of the bladder.

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34. Gunsett, A.: La roentgenthérapie du cancer de la vessie par la méthode de la dose fractionnée, Acta radiol. **13**:1, 1932.

35. Lazarus, J. A., and Rosenthal, A. A.: Myxosarcoma of the Bladder: Case Report of a Child Two Years of Age, J. Urol. **27**:695 (June) 1932.

36. Walters, Waltman, and Mulholland, S. W.: The Relation of Diverticula of the Bladder to Obstruction of the Vesical Neck, Surg., Gynec. & Obst. **55**:104 (July) 1932.

Urinary obstruction was a symptom in each case. The average duration of the symptoms was eight and seven-tenths years. Dysuria and burning on urination were usually late symptoms, and were accompanied by pain in the bladder and perineum. There was a high degree of infection of the urine in 26 of the cases. The average quantity of residual urine in the bladder was 360 cc. Residual urine was absent in only 1 case. In 10 cases the bladder was so distended as to extend above the symphysis pubis.

On the assumption that diverticula are caused by congenital weakness of the bladder that is manifested because of the obstruction, a study was made to ascertain the evidence of other abnormalities. Hernia existed in half of the cases; obesity was marked in about a third. Diabetes was present in 3 cases, and unilateral complete duplication of the renal pelvis and ureter was found in 1 case.

Diverticula of the bladder in adults practically always are seen in the presence of obstruction at the vesical neck, which undoubtedly accounts for the preponderance of the lesion in men. This series was composed entirely of men. In more than half of the cases, definite fibro-adenomatous hypertrophy of the prostate gland made prostatectomy advisable. The smaller the prostate gland was at operation, the longer the symptoms seemed to have been present. Cicatricial contraction of the vesical neck may occur, and can be remedied by a plastic procedure at the time of diverticulectomy, by a subsequent punch operation or by incision with the Collings knife.

Excision of the diverticulum is the only operation which gives uniformly satisfactory results. Extravesical excision is usually applied to large diverticula that can be separated from the surrounding structures by careful dissection. It was used in 19 of the 30 cases. If there is evidence of marked perivesical inflammation, if the bladder has been previously drained and much scar tissue is present, making extravesical dissection difficult and hazardous because of the possibility of opening the peritoneal cavity, and if the diverticulum is not too large, the transvesical method is indicated. This type of procedure was used in 5 cases.

The results were satisfactory in more than two thirds of the cases in which the diverticulum was removed. In 2 cases the outcome was fair; there was relief from most of the disturbing symptoms. Five patients continue to have dysuria. Removal of a portion of the sclerosed vesical neck by the punch operation did not always serve immediately to relieve the urinary retention. The best results were obtained in cases in which the obstruction at the neck of the bladder was thoroughly removed, either at the time of diverticulectomy or subsequently by prostatectomy or by a punch operation for an obstructing median bar.

Fistula.—Juliá [37] reported the results of transvesical intervention in 3 cases of vesicovaginal fistula. This type of fistula may be approached vaginally, transvesically or transperitoneally. Although most gynecologists prefer the vaginal method, the results are uncertain. The disadvantage of the transperitoneal route of Legueu is that it exposes the peritoneum to infection from the infected bladder. The transvesical procedure of Marion is the most simple method of approach. It is indicated in all cases of vesicovaginal fistula except those involving the neck of the bladder, when the vaginal approach is preferable.

The bladder should be opened widely, placing the separator of Legueu outside of the bladder. The posterior depressor, situated within the vesical cavity, well exposes the lower part of the bladder, which is usually the site of the fistula. Care should be taken not to include the ureteral orifices in some suture, or to cut them when dissecting the mucosa. For the deep stitches the linen type of suture used in gastro-intestinal surgery is preferable, because of its greater resistance, fineness and flexibility, which permit it to be tolerated with little reaction. In the 2 cases in which the results were successful, a linen suture was used; in the third case, which was a failure, catgut was used for both deep and superficial sutures. For the superficial stitches, particularly those in the mucosa, catgut is desirable because of its prompt resorption. There should be perfect coaptation of the sutured margins to prevent infiltration of urine between the stitches. Drainage, which is necessary after these operations, may be either urethral or suprapubic. Juliá prefers suprapubic drainage because it permits the use of a large catheter which is less likely to become obstructed. The catheter should remain in place for from seventeen to nineteen days, according to the degree of infection following intervention.

[COMPILERS' NOTE.—In any operation of reconstruction for vesicovaginal fistula, as well as for any plastic operation on the urethra, one of the most important procedures is urinary drainage by simple cystostomy, regardless of the method used to treat the lesion. This preliminary drainage is generally an important factor in obtaining the best result following a plastic operation.]

Cystitis.—Ravich and Katzen [38] stated that cystitis emphysematosa is more common among females than among males; in only 5 of the 24 cases reported in the literature were the patients males. The disease usually occurs in adult life. Although the etiology of the lesion

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37. Juliá, Serrallach: Tratamiento de las fístulas vésico-vaginales por vía transvesical. Rev. españ. de cir. y urol. **14**:159 (April) 1932.

38. Ravich, Abraham, and Katzen, Perry: Cystitis Emphysematosa: Review of the Literature with Report of an Authentic Case Terminating in Recovery. J. A. M. A. **98**:1256 (April 9) 1932.

is not definite, it is believed that bacteria are a significant factor. Macroscopically, there are gas-containing vesicles in the wall of the bladder; these may occur singly or in groups in any portion of the bladder, or may cover the entire organ more or less uniformly. They appear as transparent, rounded elevations which protrude into the lumen of the bladder. Microscopically, desquamation of the epithelial covering of the bladder overlying the vesicles is often observed. In 17 of the 24 cases there were no symptoms in the urinary tract. When such symptoms were present, they were usually due to the accompanying urologic pathologic condition aside from cystitis emphysematosa.

Ravich and Katzen reported a case in which recovery followed surgical intervention.

Surgery.—Walters [8] reported that 164 operations were performed on the bladder; 5 patients died from extensive carcinoma of the bladder during 1931 at the Mayo Clinic. Diverticulectomy was performed in 14 cases; all the patients recovered. Transurethral fulguration of intravesical tumor of the bladder was done in 114 instances without mortality.

PROSTATE GLAND

Hypertrophy.—Marion [39] stated that, in his opinion, the transvesical method of operation in chronic cases of prostatitis is preferable because of the likelihood of perineal fistulas and the difficulty of suppressing all the inflammatory lesions when the lower route is used. The procedure is indicated in chronic cases of prostatitis in which there is mild suppuration which does not respond to any medical treatment, perineal fistula and periprostatitis, calculi or hypertrophy of the gland. Urethrography should be done to confirm the diagnosis and to show any cavities or tracts which had not been suspected.

The type of intervention to be used depends on each particular case. If it is necessary to remove the lobes of the prostate gland with small abscesses, these may be easily enucleated by means of incisions that cross the entire wall of the bladder. The incision in the bladder is made immediately behind the vesical neck, following two oblique lines backward and outward, the knife being guided to a certain extent by the finger in the rectum which is orienting the lobes. When the abscesses are large and open into the urethra or form fistulas into the perineum, it is sufficient to open them widely, depressing the upper wall formed by the bladder and the tissue of the gland which incloses them. If calculi are present, the pockets which contain them should be opened and the stones removed. If suppuration in the prostate gland coincides

39. Marion, G.: De la voie transvésicale dans les affections de la prostate autres que l'hypertrophie et le cancer. J. d'urol. **33**:217 (March) 1932.

with adenoma, the more or less adherent tumor should be removed, which will open the purulent cavity lying below it. After any of these operations the cavity is packed, and a postoperative course similar to that in any ordinary prostatic case is followed.

In some cases preoperative vaccination was given. In 1 instance in which there was much suppuration and no vaccination before operation, generalized infection and death resulted. Marion expressed the opinion that surgical intervention in these cases does not entail any more risk than prostatectomy for hypertrophy of the gland. There were only 2 deaths among 74 patients so treated.

[COMPILERS' NOTE.—The advocates of the suprapubic route and the perineal route for attacking the various pathologic conditions of the prostate gland and seminal vesicles appear to be at variance. It is evident that Marion has obtained satisfactory results by the transvesical method. In many cases of chronic prostatitis and seminal vesiculitis in which there is practically no communication with the bladder, the perineal route secures better drainage with less suffering and shorter hospitalization, and prevents localized infection of the bladder and its ascent into the upper part of the urinary tract. Prostatotomy or vesiculotomy for chronic prostatitis or seminal vesiculitis was well conceived by Fuller. As Gutierrez [40] has shown in a report of 100 consecutive cases in which seminal vesiculectomy was performed without mortality, if the operation is performed extra-urethrally, extravesically and extra-peritoneally, there is no danger of complications such as Marion and other supporters of the suprapubic route have emphasized.]

Segurola [41] reported a case in which adenoma of the prostate gland recurred five years after prostatectomy. Unusual features of the case were the extreme hypertrophy of the group of precervical or anterior cells, localization of the tumor above the neck of the bladder and independent of it, attachment of the tumor to a pedicle and the fact that this occurred after prostatectomy, at which time there was no change in the cells of the anterior group. These cells, which were first described by Aschoff, not uncommonly undergo hypertrophy. Young explained why intravesical tumors of the prostate gland sometimes acquire a pedunculated form, but no cases were reported in the literature in which the reproduction of the hypertrophy was localized exclusively in the

40. Gutierrez, Robert: Later Results of Surgery of the Seminal Vesicles: Report of One Hundred Consecutive Seminal Vesiculectomies, J. A. M. A. **93**: 1944 (Dec. 21) 1929.

41. Segurola, M.: Tumor pediculado localizado por encima del labio anterior del cuello vesical y constituyendo histologicamente un adenoma prostatico en un operado de prostatectomia, con cinco anos de anterior-idad, An. de cir. **4**:344 (May) 1932.

group of ventral cells and appeared to be completely intravesical, independent of the neck of the bladder and simulating a tumor of it.

The provisional diagnosis was sessile tumor of the bladder. Because partial cystectomy was contemplated, the bladder was widely opened, and the tumor was found to be attached to a short pedicle. The growth was removed and a seed of radium was placed within the site of its implantation. The patient made an uneventful recovery. Histologically, the growth was an adenoma of the prostate gland.

[COMPILERS' NOTE.—Recurrence of hypertrophy of the prostate gland after prostatectomy is always of great interest. There are many ways to explain the failures of total prostatectomy, and the sequelae are well known. Cases of reproduction of glandular tissue in the neck of the bladder in which the same clinical symptoms have appeared as were present previous to operation have been recorded from time to time in the literature. Bransford Lewis has recently discussed this phenomenon. It is a fact that in many cases of perineal prostatectomy, for lack of proper exposure, the entire gland is not removed at the first operation, and sometimes a median or a lateral lobe is pushed back into the bladder. This is not detected during enucleation of the gland, and gives rise to a pedunculated lobe of the prostate gland. This lobe may be attached by a small bit of capsular or mucosal tissue to the roof of the neck of the bladder, resulting in definite hypertrophy with clinical symptoms such as Segurola has described. Thomson-Walker has called attention, in suprapubic prostatectomy, to the formation of tags which have been omitted during enucleation of the gland and which later undergo hypertrophy and produce definite mechanical obstruction to the outflow, and even attacks of complete retention such as occurred previous to the operation.]

Treplin and Vogel [42] reported a series of cases of hypertrophy of the prostate gland, most of which were unsuitable for open operation and in which treatment was by transurethral diathermy. These authors developed an instrument similar to a urethral catheter which has a silver band several centimeters from the tip. An eye in the tip makes it possible to determine the position of the instrument. The instrument is inserted into the bladder and withdrawn until the fluid ceases to flow, indicating that the coagulating section or silver band is in the prostatic part of the urethra. At this time the current is turned on, and for thirty seconds the prostatic part of the urethra is coagulated.

In a series of 15 cases there was no mortality, and good functional results were obtained, all patients being able to empty the bladder completely after treatment. In 4 cases there were extensive pulmonary

42. Treplin, L., and Vogel, R.: Ueber weitere Erfharungen mit der Diathermie-operation bei Prostatahypertrophie. Zentralbl. f. Chir. 59:1284 (May 21) 1932.

complications and myocardial degeneration, but the results were also satisfactory. In 3 cases of carcinoma of the prostate gland it was necessary to perform suprapubic drainage before treating the gland by this method. One patient received no benefit from the treatment; the other 2 were able to empty the bladder completely, and the suprapubic fistula eventually closed.

Davis [43] reported a summary of the immediate operative and the late functional results in a series of 411 consecutive cases of perineal prostatectomy performed under sacral block anesthesia. Nine deaths have occurred in the series. Inquiry several months after operation disclosed that 82 per cent of these patients voluntarily classified themselves as well, 17 per cent as improved and 2 per cent as unimproved. Massive delayed hemorrhage, appearing as late as the end of the second week after operation, occurred in 2 per cent of the cases.

The chief factors contributing toward maintaining a low mortality rate in prostatectomy are adequate preliminary drainage, employment of the perineal route, detailed attention to hemostasis and sacral block anesthesia. The technic of sacral block anesthesia for prostatectomy may be made sufficiently exact to eliminate entirely the percentage of failure which was formerly considered inevitable. Davis has employed sacral block anesthesia for perineal prostatectomy in 262 consecutive cases without failure of the anesthetic in a single case. All of the 411 patients received this type of anesthesia, which consisted of a caudal injection, and injection into the first, second and third posterior sacral foramina.

Walters [8] found that 22 deaths (10 per cent) occurred in a series of 227 cases in which cystostomy had been performed at the Mayo Clinic in 1931. In 135 cases the operation was performed because of urinary obstruction from hypertrophy of the prostate gland. Necropsy revealed that the causes of death were lesions such as coronary thrombosis, acute bacterial endocarditis, pulmonary embolism, coronary sclerosis with occlusion, marked dilatation of the pelvis of the kidney and ureters with renal insufficiency and embolic infarct of the lung pulmonary edema caused the death of 1 patient, aged 80.

Walters expressed the belief that the transurethral method for relieving obstruction due to so-called median bar prostatitis and contracted neck of the bladder is superior to an open operation. At present it is acceptable as a surgical procedure in cases in which there is a slight degree of adenofibromatous hypertrophy of the median and lateral lobes of the prostate gland. If there is considerable hypertrophy of the gland and the condition of the patient is satisfactory, prostatectomy done by a properly trained surgeon will have as low a mortality as any

43. Davis, Edwin: Analysis of Results in 411 Consecutive Cases of Perineal Prostatectomy. Nebraska M. J. **17**:224 (June) 1932.

transurethral procedure. On the basis of pathologic changes in adeno-fibromatous hypertrophy of the prostate gland, the obstruction is likely to recur unless the adenoma is completely removed.

Bumpus [44] stated that prostatectomy is performed primarily for correction of urinary obstruction in the urethra, rather than because of any change in the prostate gland. The operation of transurethral resection of the prostate gland endeavors to correct the obstruction by removing only the portion which obstructs and not any other tissue. When this obstruction is slight, and in a channel the diameter of which is less than 1 cm., the amount of tissue capable of causing obstruction may be insignificant, and patients have been seen whose urinary retention was completely relieved by removal of less than 1 Gm. of tissue, if such tissue completely blocked the urethra.

In a series of 96 patients with adenofibromatous hypertrophy of the prostate gland treated by transurethral methods during the last seven years, 52 were dismissed as completely relieved of residual urine, as tested by catheter. In 9 other cases there was less than 30 cc. of residual urine, although in 38 cases there was more than 150 cc. before operation, and in 17 complete retention had occurred. Of the 86 patients who are still living, 68 are satisfied with the results. Among the 18 cases in which operation was not successful, prostatectomy has been performed on 4 patients; all these operations were performed more than five years ago.

The beneficial results of the operation depend on the amount of tissue removed. Experience has shown that from 10 to 20 Gm. of tissue may be safely removed from the neck of the bladder if the associated residual urine is completely relieved as a result. If any urine is left, the presence of a denuded area in a closed viscus with residual urine and a considerable amount of electrocoagulated dead tissue gives a combination that may cause trouble. Major intravesical operations must be followed by complete drainage, and if it is necessary to resect large amounts of obstructing tissue, suprapubic cystostomy should first be done.

TESTIS, EPIDIDYMIS AND SEMINAL VESICLES

Undescended Testis.—Wangensteen [45] stated that the imperfectly descended testis is aspermatic because of its position. Before puberty the undescended testis is not unlike one in the scrotum. The scrotum serves as a thermoregulating mechanism, and a scrotal testis is normal in the adult only. The undescended testis is more likely to become

44. Bumpus, H. C., Jr.: Transurethral Resection of the Prostate Gland, Proc. Staff Meet., Mayo Clin. **7**:249 (April 27) 1932.
45. Wangensteen, O. H.: The Surgery of the Undescended Testis, Surg., Gynec. & Obst. **54**:219 (Feb.) 1932.

malignant than the normally descended one, and scrotal fixation does not diminish this predisposition to malignancy. The undescended testis, however, is not a precarcinomatous lesion, and malignant lesions of the testis are rare.

The treatment of undescended testis is placing the organ in the scrotum without injury to the testicular blood vessels. There should be adequate mobilization of the vessels of the testis for the success of the procedure. Temporary adequate scrotal anchorage should be a part of the technic; without it, retraction occurs and the testis does not grow to normal size. The best time to perform the operation of orchiopexy is when the patient is between 8 and 11 years old; to insure good functional result the operation should be done before puberty.

[COMPILERS' NOTE.—The work of Torek and Bevan on the undescended testis has been a distinct contribution to American urology. The principles of free mobilization of the spermatic cord with maintenance of testicular blood supply, together with fixation of the testis by some form of temporary or permanent anchorage in the scrotum, are well known. Retraction of the testis, as Wangensteen observed, is a frequent cause of failure and must be carefully guarded against; this is done by his procedure of temporary anchorage to the thigh. It is generally agreed that the operation offers best results if done between the ages of 8 and 11 years.]

Hepler [46] summarized the generally accepted conclusions on undescended testes as follows: The testis before puberty, in its normal position, and the undescended testis before puberty are grossly and histologically similar. The apparent atrophy of the undescended testis before puberty does not indicate that it should be disregarded or removed because it is of no value; under proper environment it is potentially a normal testis. The undescended testis of adults is aspermatic because of degeneration of the germinal epithelium, which is attributable to the constantly higher temperature to which the testis is exposed when retained in the abdomen or inguinal region than when it is afforded protection by the scrotum. If the undescended testis is properly placed in the scrotum before puberty, spermatogenesis will later take place and it will develop normally. The best age for orchiopexy is between the ages of 6 and 10 years. The testis should not be replaced before the fifth year unless there is some complication which needs correction. A normally functioning organ should not be expected if replacement is delayed too long after puberty, although the cosmetic effect may be satisfactory.

46. Hepler. A. B.: Surgery of the Undescended Testes: A Modified Torek Operation, West. J. Surg. **40**:286 (June) 1932.

The essential features of successful orchiopexy are careful and complete separation of the component structures of the spermatic cord without interference with the blood supply of the testis, and the temporary fixation of the testis to some structure outside the scrotum to prevent retraction until this tendency has been overcome. A modification of the Torek operation is described, which has given satisfactory results in 12 cases in the last year. This technic, or some modification of it, has been increasingly popular and has given complete satisfaction because the late results are as good as the early results.

Walters[5] stated that the operation of Torek and Meyer is being used more often for cases of cryptorchidism than formerly. As much length as possible is added to the cord by separation of the hernial sac and division of connective tissue joining the spermatic vessels and the vas deferens. The testis is then brought down into and through an incision in the scrotum and attached to the fascia lata of the thigh. After four weeks, the testis is dissected from the fascia lata of the thigh and the skin of the scrotum from the skin of the thigh, the testis is replaced in the scrotum and both incisions are then closed. In 200 operations on the testis and epididymis, 48 plastic operations were performed for undescended testis, in practically all of which the principle described by Torek was employed. There was no mortality. In approximately 100 cases of cryptorchidism in which this operation has been performed in the last five years, the results have been uniformly successful, and the field of applicability of the operation has been extended to include even cases of intra-abdominal testis. In only 3 cases of undescended testis last year was orchidectomy necessary.

Carcinoma of the Testis.—Chevassu[47] considered the procedure to be followed when carcinoma of the testis is suspected. A significant point in the diagnosis is the presence of a hard area in a testis apparently normal otherwise. This should be immediately confirmed by exploration with the patient under local anesthesia, at which time unusual vascularization of the albuginea would suggest malignancy. There should be no hesitation in performing exploratory orchotomy when the diagnosis is doubtful.

Toulson[48] stated that inflammatory masses occurring chronically in and about the testis may undergo hyalinization and lead to a mistaken diagnosis of new growth. Hyalin is rather commonly observed in the pleura, pericardium and spleen, but is rare in the testis. Hyalinization of a hydrocele is a state in the chronic process of the inflammation, and tends to undergo calcification.

47. Chevassu, Maurice: Diagnostic immédiat et précoce des cancers du testicule, Bull. et mém. Soc. nat. de chir. **58**:475 (March 19) 1932.
48. Toulson, W. H.: The Hyalinization of Hydrocele Sacs. J. Urol. **28**:247 (Aug.) 1932.

Carcinoma of the Epididymis.—Coleman, Mackie and Simpson[49] reported the clinical and pathologic findings in a case of primary malignant teratoma (embryonal carcinoma) of the epididymis. The neoplasm corresponded structurally to the most common form of malignant neoplasm originating in the testis. The evidence appears to be conclusive that these neoplasms have their origin in preexisting teratomas, in which one of the tissue elements undergoes malignant transformation. Removal of the testis, epididymis and spermatic cord is usually of no benefit in view of the fact that metastasis occurs relatively early in these cases.

[COMPILERS' NOTE.—Malignant tumors of the epididymis are extremely rare, only a small number having been reported in the literature. In the small series of case histories reported, these tumors are as rapidly fatal as those of teratoma of the testis. A few cases of benign tumors of the epididymis have also been reported; recently Hinman and Gibson reviewed 10 cases of sarcoma from the literature. A few angiomas of the epididymis have also been described.]

PENIS

Hypospadias.—Hagner[50] stated that incurvation of the penis in hypospadias is caused by the shortening of the fibrous tissue which, in this malformation, replaces the corpus spongiosum. A method of grafting skin for this condition is reported. The graft, including all the layers of the skin, is cut from the inner side of the thigh and placed in saline solution. A cannula is then thrust through the corpora cavernosa, care being taken to place it above the line of the fibrous tissue that causes the chordee. The cannula is then withdrawn; the skin graft is placed around it, the skin side next to the instrument, and two or three fine catgut sutures are used to bring the edges together. The cannula is reintroduced through the puncture and the graft is slipped off, two fine catgut sutures being placed at the ends to hold it in position. Two of these grafts are usually sufficient. The urine is drained by a retention catheter in the opening of the perineal or the scrotal urethra, and a sterile dressing is then applied. The grafts heal rapidly. At the end of two or three weeks a grooved director is passed through the graft and incised from within outward to the surface of the skin. The graft tends to flatten out as soon as the incision is made; after a month or six weeks the grafted area

49. Coleman, C. A.: Mackie, J. A., and Simpson, W. M.: Primary Malignant Neoplasms of the Epididymis, Surg., Gynec. & Obst. **55**:111 (July) 1932.

50. Hagner, F. R.: A New Method for Straightening the Penis in Hypospadias. J. A. M. A. **99**:116 (July 9) 1932.

can be noticed only by the difference in the appearance of the skin, while palpation at the base of the graft discloses no tendency to the formation of scar tissue.

Cecil[51] stated that in the surgical treatment of hypospadias a good result cannot be obtained without complete diversion of the urinary stream; this is brought about by occlusion of the urethra by suture. Drainage tubes, probes and other foreign bodies should not be left in the newly formed urethra. The primary operation for correction of the deformity of the penis should be done in the first two years of life. It should be complete, and no other operation should be done until it has been proved that the deformity has been cured.

Heteroplastic grafts are of no value for reconstruction of the urethra. Autoplastic free grafts, such as the use of the appendix, veins, arteries or free skin grafts, after the method of Nove-Josserand, are unsatisfactory in reconstructing the urethra. The most successful method is by the technic of Thiersch, which is applicable to all forms of hypospadias.

Epispadias with incontinence is curable in many cases. Transplantation of the ureters to the bowel should be done only in cases in which it has been impossible to reconstruct the vesical neck. The most desirable method of reconstructing the neck of the bladder and urethra is the method proposed by Young, which was described fully by Cecil.

[COMPILERS' NOTE.—Diversion of the urinary stream as an initial procedure in the surgical treatment of hypospadias is well established. Cecil's avoidance of a drainage tube or probe to splint the newly formed urethra is noteworthy. Many plastic procedures have been described to fulfil the requirements presented by the individual case. Perhaps the technic of DuPlay or one of its modifications is most often used. The technic of Van Hacker or Beck tends to constrict the penis or to increase its curvature to definite disadvantage. A preputial skin flap to form a new channel has been successfully used by Mayo and by Young. When autografts are used, the latter author prefers whole thickness grafts from the thigh.]

Carcinoma.—Leighton[52] contributed a summary of 67 cases of carcinoma of the penis. Of 24 patients who did not receive treatment, 3 died of carcinoma and 1 of an unknown cause; 19 have not been traced and 1 was operated on elsewhere. Of 43 patients who were treated, 4 had roentgen or radium therapy. Three of these died and 1 could not be traced.

51. Cecil, A. B.: Surgery of Hypospadias and Epispadias in the Male. West. J. Surg. **40**:297 (June) 1932.

52. Leighton, W. E.: Carcinoma of the Penis, with a Report of Sixty-Seven Cases, Am. J. Cancer **16**:251 (March) 1932.

Various surgical procedures were performed in 34 cases. Partial amputation of the penis was done in 3 cases, partial amputation with inguinal dissection in 5, total amputation in 1 case, total amputation with inguinal dissection in 11 cases and total emasculation in 14. Five of the 34 patients operated on have not been traced. Fourteen died, 2 after operation and 3 of recurrence; 9 lived from one month to eighteen years, death being due to causes other than carcinoma. Nineteen are living from six months to twenty-five years after operation.

According to Broders' classification of malignancy, 5 carcinomas were graded 1; 19 carcinomas, 2; 6 carcinomas, 3, and 1 carcinoma, 4. In each of the 3 cases in which death resulted from recurrence there was metastasis in the inguinal lymph nodes at operation. Five patients who had tumors graded 2 with inguinal metastasis at the time of operation are still alive and free from recurrence.

[COMPILERS' NOTE.—Carcinoma of the penis, papillary or flat usually arises beneath a tight redundant prepuce. The prophylactic procedure of circumcision in youth cannot be too greatly emphasized. Advocates of radical surgery, such as the procedure outlined by Young, and of roentgen therapy vie with one another as to the excellence of end-results. Increasing evidence shows the superiority of radium treatment if applied early and before the invasion of Buck's fascia. Here again the prognostic importance of the grade of malignancy in determining the probability of cure or of length of life after any form of treatment is noteworthy.]

URETHRA

Tumors.—Kirwin[53] stated that the most common type of epithelioma of the urethra is squamous cell carcinoma; the papillary form occurs less frequently and the columnar cell type rarely. One adenocarcinoma is recorded in the literature. In cases in which the exact site of origin was ascertainable, the growth appeared most often in the perineal or membranous portion of the urethra. The fact that squamous cell carcinoma arises in these portions of the urethra is accounted for by some writers as due either to metaplasia or to embryonal inclusion in the cell nest. There may be formation of patches of leukoplakia which later undergo malignant degeneration. The continuous passage of infected, irritating urine over a surface already injured by inflammation and the passage of instruments would inevitably produce a hyperplastic reaction. In at least two thirds of the cases reported in the literature there was a previous history of stricture, sometimes for as long as thirty years, before malignancy became evident.

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53. Kirwin, T. J.: Primary Epithelioma of the Urethra, J. Urol. **27**:539 (May, 1932.

Gonorrhea is apparently an important factor in the production of urethral carcinoma, owing to the frequency of stricture as an antecedent to the lesion. Chronic urethritis would seem likely to produce the conditions under which malignancy would develop rapidly. In some cases there was a history of the previous removal of benign papillomas. In 1 case there had been infection urethritis, and for twenty years it had been necessary to dilate the resulting stricture frequently. Guyon cited a case of urethral carcinoma in which there were multiple fistulas after urethritis of long standing, and Englisch reported a case of periurethral abscess with formation of fistula and development of a malignant lesion after three years' continuous drainage.

Difficulty in urination is the chief complaint. The urinary stream diminishes in size and volume until it is reduced to a mere dribble, and even then straining is necessary to effect partial evacuation of the bladder. Palpation usually reveals one or more hard nodules.

Kirwin reported a case in which the original lesion, close to the urinary meatus, was excised with the bipolar cautery, the metastatic inguinal nodes were removed and the inguinal wounds were treated, first by implantation of radon and later by Alpine light and deep roentgen rays. Examination after four months disclosed slight recurrence, but this was controlled by further cauterization. The patient is still in good condition.

Mercier [54] reported a case of carcinoma of the urethra of a man, aged 59. At the age of 19 years he had had urethritis, leaving contractions of the canal, which had been dilated several times. At examination only a filiform bougie could be passed into the urethra. Pus and bacteria in the urine suggested an abscess of the urinary tract. Internal urethrotomy was performed, and the abscess was drained of thick, foul pus. Convalescence was uneventful for about a month; at that time a perineal fistula was noted. The urethra admitted only a no. 24 bougie. Urethrotomy was performed again, and the fistula was widely opened. A granular mass in the bulbar portion of the urethra led to a diagnosis of squamous cell epithelioma. Resection was performed, followed by treatment with radium.

Carcinoma of the urethra in the male is rare, and is usually situated in the region of the corpora cavernosa. It is seldom correctly diagnosed at the onset of symptoms because the patients do not seek treatment until marked dysuria and pollakiuria are present or sometimes until a perineal urinary fistula has formed. Urethrorrhagia is not an early symptom. The objective symptom most often noted is a perineal or penile tumor without accompanying pain. Urethroscopy or operation is

54. Mercier, Oscar: Un cas de cancer de l'urètre chez l'homme. Union méd. du Canada **61**:336 (Feb.) 1932.

necessary to determine the diagnosis. The significant facts in this case were that an epithelioma had developed on an old stricture and that, after dilatation and urethrotomy, the stricture formed again with unusual rapidity. It is emphasized that any stricture of the urethra which does not respond to suitable treatment should be suspected of being produced by an epithelioma.

[COMPILERS' NOTE.—These pathologic lesions of the urethra, although rare, must be borne in mind, and in some instances in which there is a history of a stricture of the urethra or of other lesions which have recurred, it is important that the preoperative diagnosis be as accurate as possible. When the diagnosis is not clinically established, urethrography should be done. Gutierrez and Lowsley,[55] when reporting 6 cases of diverticulum of the urethra, found in the literature 116 cases, in most of which the diagnosis was made at operation and in many instances was followed by perineal and urethral complications for lack of correct diagnosis. The study revealed the importance of taking urethrograms in all unrecognized pathologic conditions of the urethra. This applies to primary malignant growth of the urethra and the so-called incurable cases of multiple stricture of the urethra.]

UROGRAPHY

Mark and Johnson[56] stated that 25 per cent sodium bromide is unsuitable and dangerous as a urographic medium because of the constant injury to the mucosa of the bladder, even when no undue pressure or overdistention is present, and because its action is markedly hemolytic. Sodium iodide in 12.5 per cent solution, although causing much less hemolysis than sodium bromide, produces a recognizable edema of the mucosa and irritation. Iopax in 30 per cent solution causes approximately the same degree of hemolysis as 12.5 per cent sodium iodide, but its use is unaccompanied by any mucosal or submucosal change, and there is no evidence of irritation. Skiodan (methiodal) in 20 per cent solution causes no hemolysis and is totally free from any irritating qualities.

The use of either iopax or skiodan (methiodal) eliminates the danger of bilateral pyelograms when they are necessary for renal and ureteral study. Overdistention is productive of injury and pain, even if mild solutions are used, but the real factor in causing irritation and

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55. Gutierrez, R., and Lowsley, O. S.: Chirurgische Behandlung der Harnröhrendivertikel mit Projektion, Verhandl. d. deutsch. Gesellsch. f. Urol. **8**:312, 1928.

56. Mark, E. G., and Johnson, E. T.: The Immediate Effects of Various Pyelographic Media upon the Mucosa, J. Urol. **27**:595 (May) 1932.

injury to mucosa is in the character of the drug itself and its immediate effects on the mucosa.

Wesson [57] compared the relative merits of iopax, skiodan (methiodal), and neo-iopax for intravenous urography. Neo-iopax was the most satisfactory because of the sharpness of pictures, absence of untoward reactions and ease of administration. The best neo-iopax pictures were usually made at five minutes. In cases in which rupture of a kidney, ureter or bladder is suspected, intravenous urography should be the first diagnostic procedure. In acute cases of ureteral stone the urogram on the unaffected side will be good and will show an increased density of the kidney on the affected side, but no outline or a delayed outline of the pelvis and ureter will be observed.

Intravenous urography is only one of the various diagnostic procedures, and its findings should be checked as far as possible by retrograde cystoscopy. To a certain extent it has restored a large field of medicine to the general practitioner, but the ultimate exact diagnosis should depend on the more conclusive data of the urologist.

Dourmashkin [58] stated that intravenous pyelography frequently supplies the only medium for ascertaining renal function on the affected side when there is apparently complete obstruction of the ureter by calculus. In the majority of chronic cases of ureteral stone, intravenous pyelography demonstrated perfect renal drainage. The presence of impassible obstruction is not a criterion which determines complete impaction, for in many such cases perfect drainage is revealed by intravenous pyelography. This method is of no aid in localizing calculi composed of uric acid. Open operation should not be used in any case unless its indications are clearly defined by intravenous pyelography.

URINARY ANTISEPTICS

Riaboff [59] stated that pyridium is eliminated in high concentration by the kidneys of normal subjects. If patients are in bed its elimination is considerably lower than normal. When administered by mouth it is not toxic or irritating to the genito-urinary tract. A pathologic study of organs removed from animals given pyridium in large doses disclosed no destructive or degenerative processes in the tissues. It had some bactericidal and bacteriostatic effects on Bacillus coli and

57. Wesson, M. B.: Intravenous Urography: A New Diagnostic Procedure for the General Practitioner, Urol. & Cutan. Rev. 36:296 (May) 1932.

58. Dourmashkin, R. L.: The Value of Intravenous Pyelography in the Management of Ureteral Calculi: Based on a Study of 45 Cases, J. Urol. 27:637 (June) 1932.

59. Riaboff, P. J.: A Study of Pyridium as a Urinary Antiseptic with Special Reference to Its Elimination by the Kidneys, J. Urol. 27:329 (March) 1932.

Staphylococcus aureus in water and urine. Pyridium excreted in the urine had no bactericidal or bacteriostatic effects on Bacillus coli or Staphylococcus aureus in vitro.

UROLOGY AND GYNECOLOGY

Stevens [60] expressed the opinion that the urologist should have some knowledge of gynecology and be conversant with the pathologic conditions of the abdomen and pelvis. Because of the frequent similarity of symptoms and not uncommon association of lesions of the female urinary and generative organs, examinations of both tracts is almost always indicated, particularly before surgical procedures. Vaginal examination will reveal many of the lesions of the urethra, bladder and lower third of the ureters, as well as those of the uterus, tubes, ovaries and broad ligaments. Study of 1,052 female patients with symptoms relating to the urinary tract disclosed that pathologic or physiologic conditions of the generative organs were possible or probable etiologic factors in about 25 per cent. Salpingitis is the most common pelvic condition requiring to be distinguished from disease of the urinary tract.

Injuries to the bladder and especially to the ureters during gynecologic operations are not unusual. Partial or complete retention of urine is common, and occasionally, pyelonephritis, as a postoperative complication in the majority of cases. The urethra should be thoroughly examined, since pathologic conditions are more common in this organ than in any other portion of the urinary tract. Such conditions often are responsible for symptoms suggestive of lesions of the generative organs of women. Infections and other pathologic changes of the adnexa should be eradicated in the treatment of many urologic lesions.

[COMPILERS' NOTE.—It is remarkable that gynecology and urology have been separated as specialties, since the former implies a study of the generative part of the genito-urinary system of women. No such division in practice has been made in the case of men. The Kelly school in Baltimore has long held that the two fields should be included under one specialty. Certainly the proximity of the urinary and the generative system in women and the frequency of associated disease make it imperative that the gynecologic specialist be familiar with urology, and vice versa. Stevens' presentation offers a good argument in favor of this contention.]

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60. Stevens, W. E.: *Differential Diagnosis of Pathologic Conditions of the Urinary Tract and the Female Generative Organs,* J. Urol. **27**:103 (Jan.) 1932.

ARCHIVES OF SURGERY

PLASMA CELL MASTITIS—A LESION SIMULATING MAMMARY CARCINOMA

A CLINICAL AND PATHOLOGIC STUDY WITH A REPORT OF TEN CASES

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Eight years ago my associates and I operated in a case of what was believed at the time to be mammary carcinoma. There was present a hard, diffuse mammary tumor. The nipple was retracted. The breast had the peau d'orange appearance typical of carcinoma. The axillary nodes were much enlarged and quite hard. There was no question in the minds of the several clinicians who examined this patient as to the diagnosis of carcinoma, as nearly all of the classic diagnostic signs were present. A radical amputation was performed. Examination of the specimen later in the laboratory, to our complete surprise and chagrin, revealed no cancer. Dr. Ewing, after making a careful study, rendered the diagnosis of "plasma cell mastitis," a term entirely new to us. He named this lesion plasma cell mastitis on account of the overwhelming preponderance of the plasma cell. This cell is not prominent in the more common forms of chronic mastitis and other conditions of the breast, except as the occasional stray cell; but in this lesion there are broad sheets of plasma cells. In addition to this, the microscopic slide shows "remarkable atypical proliferation of lining cells of ducts which considerably resembles carcinoma" (Ewing). A subsequent scrutiny of the details of the case left us in somewhat of a quandary as to how to avoid making a similar diagnostic error, provided such a case again came into our hands. During the course of the past eight years ten such cases have come under our observation, and an analysis of these cases has convinced us that this group, difficult of diagnosis for both clinician and pathologist, represents a distinct clinical entity. Our studies of these cases lead us to the conclusion that plasma cell mastitis is a disease of the breast which gives a characteristic history and possesses features which usually make a clinical diagnosis possible even though difficult.

The object of this report is: (a) to establish the condition in this group of cases as a distinct clinical disease among mammary lesions, (b) to place the diagnosis on a more cleancut basis and (c) to prevent performance of grave and possibly unnecessary operations.

Literature on the subject of mastitis is especially voluminous. This seems, however, to be the first report on this type of mastitis, except the article on the subject to be found in the recent book by Cheatle and Cutler, "Tumours of the Breast," which is based on a study of the ten cases herein reported. The reader is referred to this article.

At times the diagnosis of mammary cancer is easy even for the novice; but at other times it is impossible for one possessing an extensive experience to be sure of the exact nature of the lesion. The difficulty of diagnosis in this group of cases will be emphasized by the fact that six of these ten cases were diagnosed as cancer by several men who have a large experience in the diagnosis of cancer.

In general, the present difficulty with clinicians in arriving at a correct diagnosis of diseases of the breast is that they too quickly conclude that the lesion is cancer, provided one or more of the diagnostic points are present, such as: retraction of the nipple, skin attachment, peau d'orange appearance, hardness and irregularity. They do not give sufficient consideration to the fact that certain benign lesions give some of the signs generally considered to be characteristic of mammary cancer. Since women now present themselves for examination much earlier than previously, the difficulties of diagnosis have greatly increased. It is therefore most important that added consideration be given to each one of the diagnostic points and that the most exact history possible be elicited.

Clinically, the two most common and difficult lesions to be differentiated from cancer are: (*a*) a localized area of chronic mastitis and (*b*) fibro-adenomas in young women.

It may be helpful at this point to give a list of those benign lesions which at times simulate carcinoma and occasionally give one or more of the signs of cancer such as skin attachment, retraction of the nipple, elevation of the breast, peau d'orange appearance or irregularity of the contour of the breast. They are the following: (1) traumatic fat necrosis,[2] (2) plasma cell mastitis, (3) chronic lactation mastitis,[3] (4) subacute inflammatory mass, (5) tuberculous mastitis, (6) gumma[4] and

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1. Cheatle and Cutler: Tumours of the Breast, Philadelphia, J. B. Lippincott Company, 1931, p. 298.

2. Lee, Burton J., and Adair, Frank E.: Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Ann. Surg. **72**:189 (Aug.) 1920; A Further Report on Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Surg., Gynec. & Obst. **34**:521 (April) 1922; Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Ann. Surg. **80**:670 (Nov.) 1924.

3. Cohn, L. Clarence, and Bloodgood, J. C.: Chronic Lactation Mastitis, Suppurative and Non-Suppurative, Am. J. Cancer **16**:487 (May) 1932.

4. Adair, Frank E.: Gumma of the Breast: Its Differential Diagnosis from Carcinoma, Ann. Surg. **79**:44 (Jan.) 1924.

syphilitic mastitis, (7) deep abscess (occasionally), (8) cyst (infrequently), (9) intracannicular fibro-adenoma (rarely), (10) traumatic mastitis and (11) benign lesion such as fibro-adenoma or papillary cyst adenoma lying within the areola.

In this list of eleven benign lesions it is to be noted that seven are of various forms of mastitis. The diagnosis of chronic mastitis of the simple forms (hypertrophic, cystic and fibrous) is usually easy as it is more commonly bilateral and the entire gland is involved. One is able to pick up the breast as a whole, the edge of which is sharply defined and, as has often been said, like the edge of a saucer.

The natural history of plasma cell mastitis should be divided into two stages:

(*a*) The acute phase. Unfortunately, the clinician rarely has the opportunity to examine the patient during this early phase because the acute symptoms such as pain, discomfort and tenderness are of such a mild degree that the patient infrequently seeks medical advice. The lesion does not proceed to abscess formation. There is a mild degree of local heat, tenderness and discomfort. The condition occurs spontaneously in a nonlactating breast. The acute process gradually subsides leaving the breast the seat of a residual, nontender tumor.

(*b*) Residual phase. This phase varies in duration from several weeks to several months after the appearance of the acute phase. The presence of a mass (fig. 1) brings the patient to the physician. He finds that the mass is not tender to palpation; it may be sharply localized or a diffuse thickening; it is firm; there may or may not be a discharge from the nipple; if present, it is watery or creamy and on microscopic examination reveals cellular detritus, mucus and desquamated degenerating lining cells. Pumping the breast with a breast pump produces this discharge over long periods if continued. Edema is frequently present over the tumor or in the dependent portion of the breast, giving the peau d'orange appearance. The nipple is retracted. Enlarged firm axillary nodes are usually present. Acute and subacute inflammatory signs are completely lacking. At this stage the lesion closely simulates mammary carcinoma.

The clinician is practically forced by the preponderance of the multiple signs of carcinoma, to arrive at a diagnosis of cancer unless he carefully considers the preceding history of the case.

Just as it is true that the differentiation of mammary cancer from traumatic fat necrosis [2] is impossible except by a detailed scrutiny of the preceding history of a competent producing injury, so it is true in plasma cell mastitis that one must rely on the antecedent history of inflammation.

As a rule, in our cases, even though the breast was nonlactating (with one exception), there was a history of acute inflammation accompanied by redness, tenderness and discomfort. This is the most important single point in the history. In our later cases we felt capable of making a correct diagnosis. In one of them we correctly suspected the exact pathologic condition for as long as two years; but as so little change took place in the tumor itself, we felt forced to capitulate from our position of frequent observations and operate in order to be certain of our diagnosis. This was before the days when we began to make such valuable use of aspiration[5] and punch[6] biopsy for assistance in diagnosis.

Another of our patients was under observation for two years. We thought the history so typical and the lesion so characteristic that we felt confident of the diagnosis of plasma cell mastitis. This patient was

Fig. 1 (case 10).—Photograph showing slight discoloration or duskiness of the left breast; also retraction of the nipple. The affected breast is heavier than the right, and there is a diffuse hard thickening in the outer half and a peau d'orange appearance. One large axillary node was present. It is five and a half years since the only pregnancy. The patient was under observation for two years before operation.

later operated on in another institution in New York City for cancer, the radical amputation being done. The slides were sent to us, and the condition proved to be plasma cell mastitis (fig. 1).

COURSE

It is of great importance and interest to know exactly what happens to the tumor if left alone. In the two foregoing cases, we have had a

5. Martin, Hays E., and Ellis, Edward B.: Biopsy by Needle Puncture and Aspiration, Ann. Surg. **92**:169 (Aug.) 1930.

6. Hoffman, William J.: New Technic and Instrument for Obtaining Biopsy Specimens, Am. J. Cancer **15**:212 (Jan.) 1931.

rare opportunity to study its course. To our surprise practically no change took place for two years. The tumors seem to have no tendency to resolve spontaneously. Even the use of the breast pump over a considerable period had but little influence, in spite of the fact that one could nearly always obtain some secretion from the nipple ducts.

We present no evidence that plasma cell mastitis is a true forerunner of cancer; but, on the other hand, there is no evidence that it is not. In general, it appears to take a long time for the etiologic factors actually to produce a cancer of the breast. No one is certain what would transpire in this particular tumor over a period of ten or fifteen years if left alone. The chemical irritation of the retained puriform material in all likelihood results in the proliferation of the lining epithelium until there are sometimes as many as six or eight rows of hyperchromatic epithelial cells. This would definitely place the lesion in the "precancerous" group in the usual interpretation of that term. We have had the unusual experience of watching two cases for a period of two years without cancer developing, but even so, a reasonable attitude toward this lesion would be to regard it as one capable of later developing into cancer. Provided this assumption is justifiable, it should then be treated as other precancerous lesions, by removing the mass itself and leaving the rest of the breast untouched.

ANALYSIS OF TEN CASES

Age.—The age incidence in the ten cases is from 29 to 44 years. Although it is true that the average age is 36.3 years, which is well below the decade (from 50 to 60 years) when most mammary cancers develop, still any one with experience does not hesitate today to render a diagnosis of mammary cancer in the decade of 30 to 40 years or younger. The average younger age of these patients, therefore, should be of some aid in the diagnosis.

Duration Since Last Lactation.—The duration of time since the last lactation seems to have no bearing on the etiology. In fact, in the majority of instances it was a period of several years since the last lactation. In one case, it was nine years. If the one instance of an actually lactating breast were excluded, the average time since the last lactation would be nearly four years.

Previous Pregnancies.—In no instance did plasma cell mastitis occur in an unmarried woman. With the exception of case 8, in which there was one miscarriage, there was an average of nearly four previous pregnancies in each case. This suggests strongly that improper drainage of the breast has an important bearing on the etiology.

Symptoms.—As a rule, the presence of a lump brought the patient to the physician. In going into the history of the patients, it is interesting

to note that they commonly had previously complained of a pain localized in the region of the lump. Pain was the first symptom noted by the patient, and it was frequently accompanied by localized redness and also at times by a discharge from the nipple. The patients stated that even in the acute stage the breast was not especially tender on palpation. The patient in case 9 had redness and tenderness which subsided under cold applications, leaving a residual hard lump. The lack of symptoms which bother the patient is striking in this disease.

Nipple Discharge.—In seven of the ten cases there was either a spontaneous discharge at the nipple or a discharge produced by gently stroking the breast toward the nipple. As a rule, the material was thick and typical of stagnated dilated ducts. In case 3, either by stroking the breast or by pumping with a breast pump, there was consistently obtained from the identical six ducts a thick creamy material. From the breast of the patient in case 2 a test tube full of creamy material was obtained at the first pumping, and up to the date when a mastectomy was performed we were able to obtain some of this thick material. In case 1, the material was yellow and purulent. The sign of a discharge from the nipple is of definite aid in the diagnosis of plasma cell mastitis.

Weight.—As a rule, the involved breast is heavier than the opposite unaffected breast. This, however, is true of carcinoma and is therefore of no aid in the differential diagnosis from cancer.

Retraction of the Nipple.—This sign is commonly positive in cancer of the breast. In our ten cases of plasma cell mastitis, it was definitely positive in eight (80 per cent), and in two cases the history did not mention this point. It seems to be a more consistent sign in plasma cell mastitis than in mammary carcinoma.

Skin Adherence.—The tumor was adherent to the skin in six of the ten cases (60 per cent). In cases 4, 6 and 9 the sign was very marked.

Peau d'Orange Appearance.—In four of the ten cases a definite statement was made that this sign was positive. No mention is made on this point in several cases.

Tumor.—The mass was always either firm or hard. It varied from a discrete, sharply outlined mass to a firm ill defined but localized process. The largest mass was that in case 3, measuring 8 by 8 by 10 cm. The lesions averaged approximately from 4 to 5 cm. in diameter.

Axillary Nodes.—In eight of the ten cases the axillary nodes were enlarged and hard. In case 8, it is stated that "there is a chain of hard nodes extending from the tail of the breast across the axilla." In case 4, it is stated that "there is a hard mass in the right axilla 4 cm. in diameter." The presence of enlarged hard nodes (80 per cent) is therefore more common than in cancer.

Transillumination Test.—In only two of our cases was this test used. In case 10, the breast was opaque to transillumination; in case 5, the test was negative. This test was not sufficiently used to enable us to state what its value would be in diagnosis.

Preoperative Diagnosis.—In two of our later cases (cases 2 and 10) the correct diagnosis of plasma cell mastitis was made. In case 5, the diagnosis of mastitis nodule was made, and in case 7, tuberculous mastitis. In five cases a positive diagnosis of cancer was rendered; in case 6, the pathologic condition was thought to be carcinoma. In case 9, the case was classified as a primary inoperable mammary carcinoma, and to add to the confusion a roentgenologic report of the chest was returned
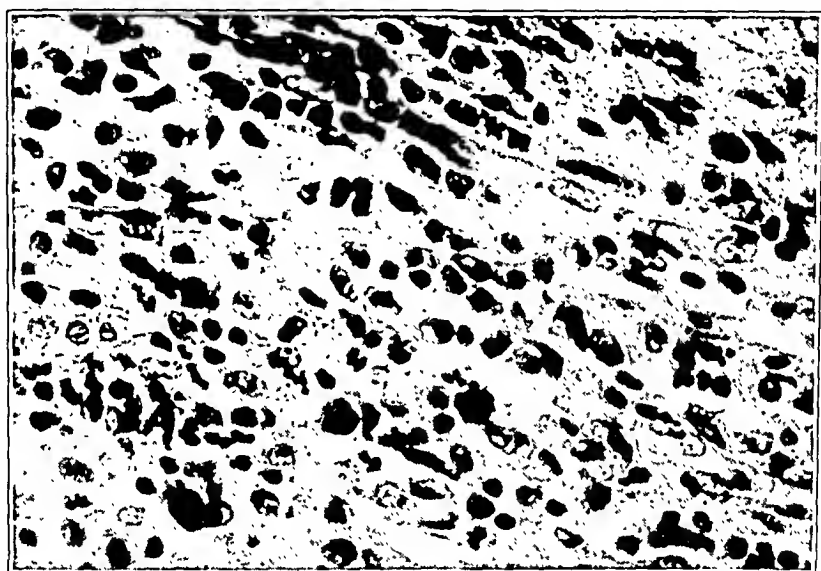
Fig. 2 (case 2).—High power photomicrograph showing infiltration with plasma cells. The cytoplasm is granular with eccentrically placed nuclei.

"evidence of metastasis." In this case several large axillary nodes, a pig-skin appearance, skin attachment, retraction of the nipple and a hard tumor were present. It was a textbook example of a case giving nearly all the classic signs of cancer, and on the signs alone one would have been forced to render such a diagnosis. However, the patient's history stated that "redness and tenderness were present for three weeks, subsiding under cold applications, leaving a hard lump." This important history of a lump residual after a preceding inflammatory process is the only factor that makes diagnosis possible in this disease. This point cannot be overemphasized in the diagnosis of plasma cell mastitis.

Treatment.—In each of the ten cases the diagnosis could have been established and the patient cured by the local removal of the tumor—a

small and simple operation. Instead of this, in eight cases, mastectomy was performed, while in only two local operations were used. The latter was due to the fact that we paid especial attention to the history of a preceding inflammatory process. Since the proper line of treatment rests on a correct diagnosis, it is obvious that the exact diagnosis of this condition will save many patients from an unnecessarily large operation. Incidentally, in statistical studies of end-results it is probable that some "cures" include some cases of plasma cell mastitis.
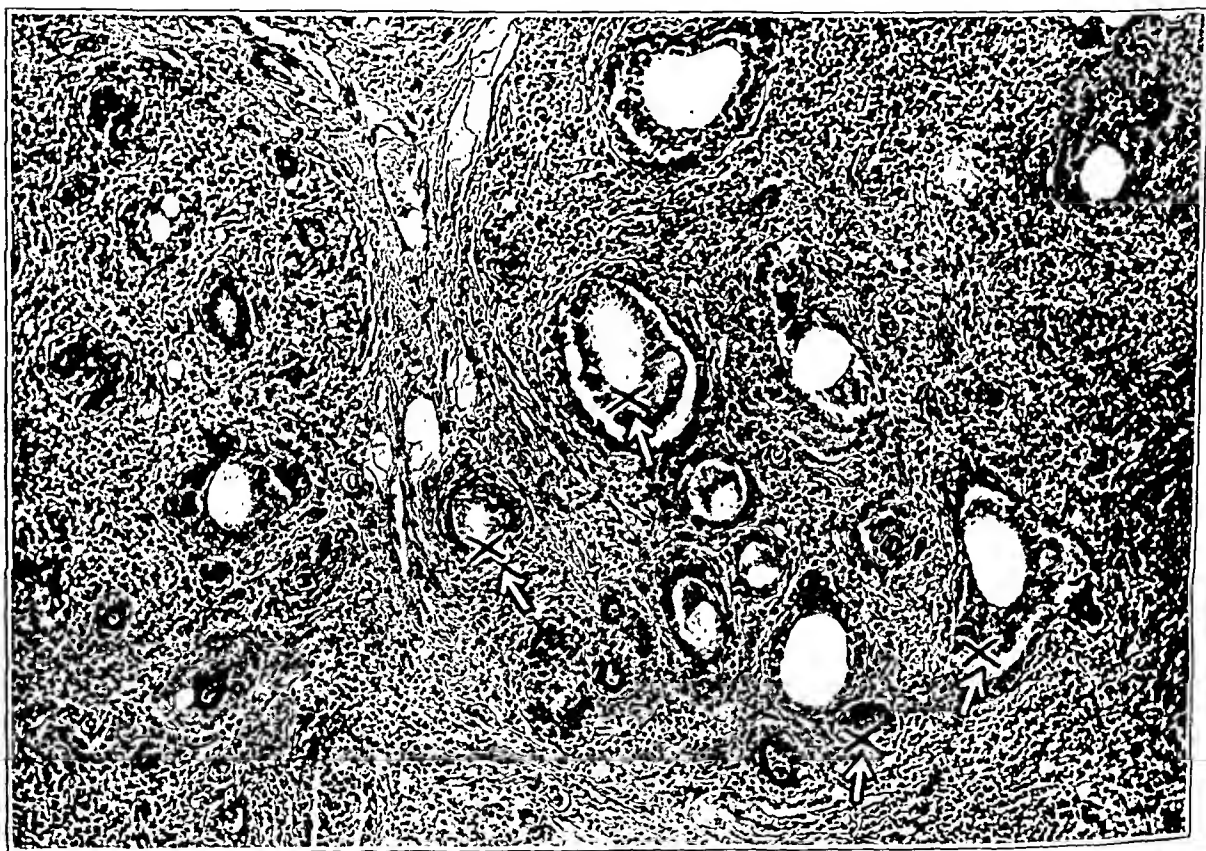
Fig. 3.—*Photomicrograph showing the heaping-up of the layers of lining* cells characteristic of plasma cell mastitis. Certain ducts indicated by crosses are completely filled with hypertrophic cells suggesting comedocarcinoma.

Pathology.—There are three outstanding characteristics of this lesion: (a) Marked infiltration by the plasma cell (fig. 2). This cell is of rare occurrence in lesions of the breast. It has granular cytoplasm with an eccentrically placed nucleus. It is thought by some to be a wandering blood corpuscle that occurs in certain chronic lesions. In plasma cell mastitis the cells occur in broad sheets, invading the ducts, the walls and the interstitial tissues.

(*b*) Proliferation of the cells lining the ducts. They pile up six to ten rows deep, with hyperchromatic epithelium. This gives an appearance at times difficult to distinguish from comedocarcinoma (fig. 3).

(*c*) Formation of giant cells (fig. 4) from these proliferating lining cells. The presence of these giant cells together with their arrangement at times makes differentiation from tuberculous mastitis puzzling.
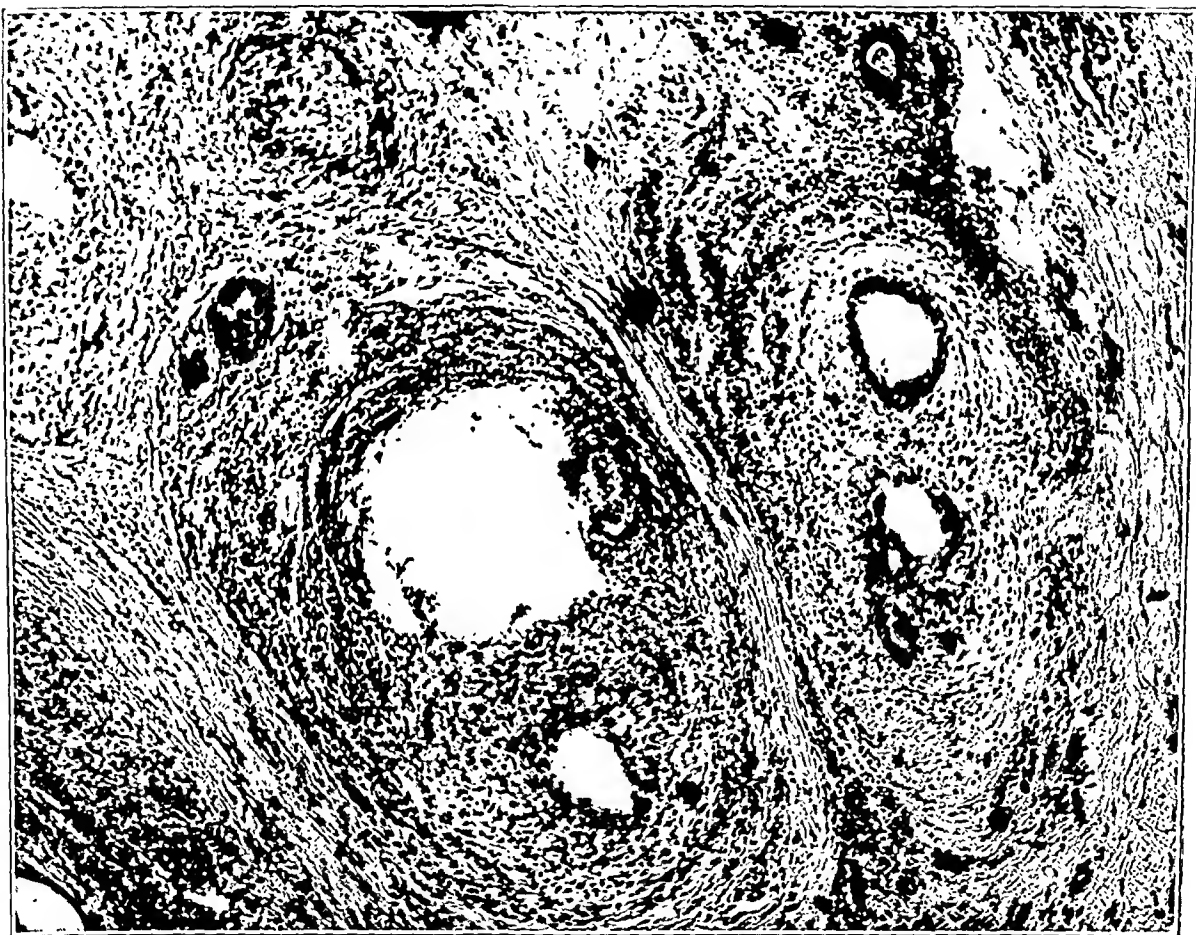
Fig. 4.—Photomicrograph showing a tremendous heaping-up of duct lining cells almost filling the large ducts.

Case 7 presents the clinical appearance of tuberculosis of the breast (fig. 5). An abstract of the ten cases is given here.

The pathologic reports are of such interest and value, especially to pathologists, that Dr. Ewing's exact descriptions are quoted in detail.

Case 1.—A. R., aged 44, had had four children, eight years elapsing since the last lactation. She came for examination on account of a lump in the breast.

There was a purulent yellowish discharge from the nipple. The breast was distorted in shape. The nipple was retracted and fixed. A tumor measuring 6 by 6 by 6 cm. lay behind the nipple. Axillary nodes were present. A preoperative diagnosis of carcinoma was made, and a radical amputation was performed.

"The large ducts are distended with pus and the walls infiltrated with many plasma cells. The prominent feature is the presence of many small ducts moderately filled with pus lined by very hyperplastic and hypertrophic epithelial cells, somewhat resembling beginning carcinoma, except that the cells are not hyperchromatic; about these ducts there is a rich infiltration of plasma cells, but no wide areas of diffuse plasma cell infiltration in this breast. There are many giant cells including fat globules. Extensive hyperplastic lymphadenitis."

CASE 2.—K. S., aged 40, had had five pregnancies, twenty months elapsing since the last one. Although painless to palpation, some sticking pains were experienced in the left breast. On pumping with a breast pump, a large test tube of creamy material was obtained. The left breast was much heavier than the right. The nipple was retracted. There was skin adherence and a peau d'orange appearance. The tumor measured 7 by 8 by 7 cm. Many large hard axillary nodes were present.

Fig. 5 (case 7).—The appearance of a breast with a condition simulating tuberculosis. There is wide area of skin infiltration, retraction of the nipple, discoloration and marked irregularity with a suggestion of an old healed sinus.

There was no elevation of temperature. The leukocyte count was normal. A preoperative diagnosis of plasma cell mastitis was made, and mastectomy was performed.

"This is a typical case of focal and diffuse plasma cell mastitis in which many leukocytes and lymphocytes are mingled with plasma cells. The infiltrated areas represent ducts and measure from 1 mm. to 1 cm. in diameter. The epithelium shows marked hyperplasia but terminates in the formation of many giant cells."

CASE 3.—R. C., aged 44, had had eight pregnancies, two years elapsing since the last lactation. Eight months before she was seen by us she noted a lump in the breast, but felt very slight pain. When the breast was stroked toward the nipple or when it was pumped, a creamy material came through six ducts. The nipple was retracted. A mass was present measuring 10 by 8 by 8 cm., the size of a lemon. Large axillary nodes were present. A preoperative diagnosis of carcinoma was made, and mastectomy was performed.

"This is a rather typical case of plasma cell mastitis. There are broad areas in which the ducts are obliterated by diffuse exudate of plasma cells. The epithelial cells are degenerating, and there are many giant cells containing lipoid material; there are comparatively few polynuclear leukocytes. Most of the epithelial cells

are mingled and lost among the plasma cells. There is moderate reactive fibrosis about some lobules. The giant cells are at times very numerous and somewhat resemble miliary tubercles."

CASE 4.—M. W., aged 40, had had three pregnancies. At the time of examination the breast was lactating, the patient having had a child four weeks previously. Two days before the birth of the child she noted pain in the breast and the presence of a lump. The skin over the lump was red. This was aspirated twice, but only serum was obtained. There was marked skin adherence. A tumor was present measuring 8 by 4 by 4 cm. A mass was present in the right axilla measuring 4 cm. in diameter. The patient was examined by ten physicians, and the diagnosis was made of a probable carcinoma in a lactating breast. A local removal of this mass was made, and a frozen section immediately examined.

"Material received consists of a mass of tissue size of small orange, and containing mostly dense translucent tumor-like tissue surrounded by a zone of fat tissue. The mass has all the density and resistance of carcinoma. On section there are many peculiar ochre yellow points and spots 1 to 3 mm. wide which project prominently as from pressure. These xanthomatoid foci are soft not semifluid, not purulent, but not firm enough for tumor tissue. In the densest portions of tissue there are no chalky streaks, but much of the dense tissue appears cicatricial and very suspicious of carcinoma of rapid growth.

"Microscopic sections show as the main features numerous foci, very cellular and composed of large rounded and polyhedral cells distended with lipoid material and often containing a great many polynuclear leukocytes and miliary abscesses. All these foci contain a great many plasma cells, which infiltrate the tissue widely. These fatty foci are the protuberant xanthomatoid areas mentioned in the gross. The glandular and duct epithelium seems to disappear in the mass of polyhedral cells and plasma cells and nowhere are there any definite foci or sheets of carcinoma cells. Yet in many less altered lobules the acinar cells are rather atypical and hyperchromatic. The outlying tissue contains many breast gland lobules which show the changes of lactation.

"*Diagnosis.*—Subacute suppurative and plasma cell mastitis in a typical case of focal and diffuse plasma cell mastitis."

CASE 5.—C. B., aged 32, had had one child, nine years elapsing since the last lactation. A lump had been present in the right breast for one week. The patient had had some pain in this breast for a month. There was a discharge from the nipple. The ducts all felt thickened. The nipple was markedly retracted. The breasts were asymmetrical, and the right breast was very hard. A small lump measuring 1 by 1 by 1 cm. was present in the right breast. No axillary nodes were present. The transillumination test was negative. A preoperative diagnosis of mastitis was made. The local removal of the mass was performed.

"Specimen consists of a fragment of tissue measuring 4 by 2.5 cm. composed of fat and fibrous tissue. At one point there is an area of denser fibrous structure measuring 0.5 cm. with one or two chalky streaks. Sections of two small ducts show the usual appearance of epithelial proliferation and degeneration with plasma cell infiltration."

CASE 6.—A. K., aged 32, had had five children, three years elapsing since the last pregnancy. Four months before she was seen by us she noted a lump in the breast and secretion at the nipple. Some pains were present over the lump. The discharge from the nipple was watery. The skin was markedly adherent to the tumor. The mass measured 6 by 4 by 4 cm. The peau d'orange appearance was present. A preoperative diagnosis of probable carcinoma was made, and mastectomy was performed.

"Remarkable atypical proliferation of lining cells of ducts which considerably resembles carcinoma but the cells are hydropic and degenerating. Many giant cells."

CASE 7.—A. T., aged 39 years, had had four pregnancies, three years elapsing since the last one. One year before she was seen by us she had pain in the left breast accompanied by redness. This disappeared in two weeks. Two weeks before she had a dull pain in this breast and found a lump present. There was a sinus near the nipple. The nipple was retracted. Marked skin adherence was present. The mass measured 5 by 6 by 3 cm. Enlarged nodes were present in both axillae. A roentgenogram of the chest was negative for tuberculosis or cancer. A peau d'orange appearance was present. A preoperative diagnosis was made of tuberculous mastitis (fig. 5), and mastectomy was performed.

"In this case the plasma cell exudate is limited to walls of ducts; the epithelial proliferation is very marked and at some points resembles comedocarcinoma. More often the proliferating epithelial cells degenerate into giant cells. Guinea-pig inoculation indicated."

Fig. 6 (case 8).—Photograph showing a mass in the right breast measuring 8 cm. in diameter. The nipple is retracted; the breast is elevated and irregular in outline; skin attachment is present. There is "a chain of hard axillary nodes extending across the axilla." It is a typical case of plasma cell mastitis.

CASE 8 (fig. 2).—C. M., aged 29, five months before she was seen by us had had a miscarriage. Following this there was caking of the breast. One month ago she noticed a lump which had been increasing in size. It was not tender. There was a discharge at the nipple. The breast was elevated and larger than the opposite breast. The nipple was retracted, and skin attachment was present. There was a mass measuring 8 by 8 by 8 cm. and some smaller lumps about this. A chain of large nodes extended from the tail of the breast across the axilla. A roentgenogram of the chest was negative. The diagnosis of carcinoma was made, and the patient was given a series of radium packs. Mastectomy was then performed.

"Main lesion surrounds and involves the large ducts which are filled with puriform material and epithelial detritus. There is a rich wide periductal infiltration of plasma cells, but no diffuse areas of infiltration. Many giant cells. Stain for tubercle bacillus negative."

Case 9.—P. G., aged 31, had had three children, one and a half years elapsing since the last lactation. Three months before coming to us there were redness and tenderness in the breast, which subsided under cold applications, leaving a hard lump. There was no discharge at the nipple, which was markedly retracted. The tumor was adherent to the skin. The mass measured 8 by 6 by 6 cm. Several large axillary nodes and a peau d'orange appearance were present. A diagnosis was made of a very cellular, highly malignant carcinoma. The patient received a series of radium packs. Radical mastectomy was performed.

"Gross diagnosis suggestive of tuberculosis. The lesion consists of dilatation of many large and small ducts by puriform material containing many plasma cells and exfoliated epithelium; there are very few polynuclear leukocytes. About the ducts there is rather wide plasma cell infiltration. There are many giant cells of all sizes. Hyperplastic lymphadenitis."

Case 10 (fig. 1).—F. S., aged 32, had had one child, five and a half years elapsing since the last pregnancy. Symptoms began with intermittent pain in the left breast which had been present for one year. There was no discharge from the nipple. The left breast was markedly heavier than the right. The nipple was retracted. A pig-skin appearance was present. There was a diffuse thickening throughout the outer half. One large hard node was present in the axilla. The breast was opaque to transillumination. Our diagnosis was plasma cell mastitis. The patient was urged for a period of two years to have this diagnosis confirmed by operation. At the end of this time she went to another hospital where a radical mastectomy was performed with the diagnosis of carcinoma. The slides were loaned to us, and Dr. Ewing, after examination, stated it was a typical case of plasma cell mastitis.

Bacteria.—The picture afforded by plasma cell mastitis frequently suggested that careful bacteriologic studies be carried out. Unfortunately, these studies were made in but four of our cases. In case 1 there was obtained "a pure growth of a large coccus, not identified." In another case there was "a rich growth of a large coccus growing in fours and pairs laterally dividing." In two cases the lesion so closely simulated tuberculosis that guinea-pig inoculations were carried out. Both cases proved negative for tuberculosis. Among other phases of the disease process is the interpretation of the presence of bacteria and the bearing on the etiologic factors discussed by Dr. Ewing.

Pathologic Interpretation (by Dr. James Ewing).—"From a survey of the present material it appears that we are applying the term plasma cell mastitis to a special group of cases which belong in the general class of chronic or subacute suppurative inflammation of the duct system of the breast. These cases differ from the ordinary suppurative mastitis in the absence of definite abscesses and generally in the wide extent of the process. The process is also much less acute and the productive element much more pronounced than in suppurative mastitis. These facts indicate that bacterial infection plays a less prominent rôle and chemical irritation a more prominent rôle than in suppurative mastitis. In the particular group of cases which has attracted our attention the plasma

cell infiltration is extremely abundant and widespread, producing rather bulky tumor masses which clinically resemble active carcinoma, and even under the microscope may be difficult to distinguish from cellular carcinoma.

"The main gross anatomic feature is the presence of many much thickened ducts, which are filled with puriform material, and may extend over a large segment or nearly the whole of the breast. In the most characteristic cases the cellular exudate is diffuse, making a broad opaque, sometimes, yellowish tumor-like mass, in which the distended ducts are less obvious or even not visible. These are the cases which resemble carcinoma, but as a rule, there are small foci of puriform softening which are not found in carcinoma.

"The plasma cell exudate begins in the walls of the ducts and extends between acini in adjoining lobules when the process becomes diffuse. Polymorphonuclear leukocytes are present in variable numbers, but are often quite scanty. The phagocytosis of fat is a prominent feature and many of the cases show a great many large plasma cells engorged with fat and resembling xanthoma. These areas have a yellow color.

"Proliferation of the lining epithelium is a peculiar and prominent feature. The affected ducts are lined by from six to ten rows of large somewhat hyperchromatic epithelial cells, which often raise the suspicion of carcinoma of the duct. Yet the later progress of these proliferating cells ends not in carcinoma but in generation fragmentation and formation of giant cells of all sizes. Many of the giant cells and degenerating epithelium produce structures which closely resemble tuberculosis. Usually the foreign body nature of these giant cells is obvious because they usually contain much fat. Stains for tubercle bacilli are negative, and guinea-pig inoculations are also negative. The appearance of the proliferating epithelium in the early or milder stages of some cases strongly recalls the appearance of comedocarcinoma. It seems probable that comedocarcinoma arises under much the same conditions, but only when the chemical irritation is more prolonged and less severe. In a few cases the proliferating epithelial cells produce many small slightly hyperchromatic giant cells, a picture which again approaches that of large cell carcinoma.

"Bacteria have been isolated from several cases, but the exact identity of the strains have not been determined nor their exact relation to the inflammatory process. Usually the bacteria are large cocci growing in pairs or short chains. They are never very numerous, and some cultures are negative. It may therefore be concluded that while bacterial infection is probably a necessary factor in the process, its influence is less prominent than the chemical effect of decomposing fatty material."

SUMMARY

A study is made of a lesion of the breast which we term plasma cell mastitis. Ten cases are analyzed. This lesion is difficult to distinguish from mammary cancer by clinical signs alone. The signs of cancer are present, such as hardness of the tumor, retraction of the nipple, skin attachment, pean d'orange appearance and axillary nodes. With such signs present, the only possibility of arriving at a correct diagnosis lies in the evaluation of the characteristic history. The typical history is that at some preceding date an inflammatory process was present in a nonlactating breast, which process was accompanied by redness, mild tenderness and mild discomfort. As the symptoms of the acute phase pass off, a residual hard mass remains. This mass is not tender or painful. In eight of our ten cases, mastectomy was performed because of the difficulty of diagnosis. The lesions had most of the signs of mammary carcinoma. The present analysis of our cases shows, however, that this is a diagnosable lesion clinically. The microscopic interpretation is very puzzling, as at times the lesion closely simulates comedocarcinoma and at other times tuberculous mastitis. It is a precancerous lesion and should be treated by local removal only.

SURGICAL ATTEMPTS AT INCREASING SUGAR TOLERANCE

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CHICAGO

An attempt to increase the utilization of carbohydrates by surgical means may follow various courses. It may try to stimulate the formation of islets in the pancreas and increase the insulin output of the gland. If one regards the insulin deficiency as the primary cause of diabetes, an increase of insulin production would be highly desirable. Minkovski's [1] belief that the diabetic organism is unable to utilize carbohydrate has been greatly strengthened by the isolation of insulin, and seemingly gave the final blow to the alternate theory of diabetes, emphatically upheld by von Noorden [2] since 1910, namely, that hyperglycemia and glycosuria are due to an overproduction of sugar, owing to a hyperirritability of the sugar-producing apparatus in the liver. This theory naturally emphasizes the nervous regulation of carbohydrate metabolism and would call for an attack on the nerve supply of organs that are effecting the utilization of carbohydrates. Our surgical attempts were shaped to conform to both theories, and we are presenting a summary of our efforts in both directions.

METHODS OF STUDY

In previous communications [3] we have described various trials with oral, intraperitoneal and intravenous administration of dextrose to determine sugar tolerance.

1. Minkovski, O.: Untersuchungen über den Diabetes mellitus nach Exstirpation des Pankreas, Arch. f. exper. Path. u. Pharmakol. **31**:85, 1893.

2. von Noorden, C., and Isaac, S.: Die Zuckerkrankheit und ihre Behandlung, ed. 8, Berlin, Julius Springer, 1927, p. 216.

3. de Takáts, G.: Correlations of External and Internal Pancreatic Secretion: I. General Considerations and Review of the Literature, Arch. Surg. **19**:771 (Nov.) 1929; II. The Histologic Changes in the Isolated Tail of the Pancreas, ibid. **19**:775 (Nov.) 1929. de Takáts, G., and Nathanson, I. T.: III. The Effect

By far the most accurate and constant data were obtained with the method of Woodyatt, Sansum and Wilder,[1] who used an electric pump to administer sugar solutions at timed rates. All dogs were on a standard kennel diet and were completely relaxed, in a basal state, during which a continuous injection of 5 per cent dextrose was given for one hour. Excitable dogs or dogs that were difficult to train to lie quietly for an hour were rejected. The autoclaved, 5 per cent solution of Pfanstiehl dextrose was passed through a waterbath with a glass coil, so that the temperature of the solution was even throughout the experiment. Urine was then collected for twenty-four hours, and the sugar, if present, was determined by Benedict's method. From two to three preoperative determinations were made. The normal dog, completely relaxed, shows a sugar tolerance of from 1.6 to 1.8 Gm. of dextrose per kilogram per hour, but most dogs, after several determinations, may show a tolerance of from 1.8 to 1.9 Gm. per kilogram of body weight, which amount, if injected intravenously for an hour, will fail to produce a glycosuria. In many of the later experiments, blood sugar determinations were also made at the beginning and at the end of the injection, and were followed up to four hours after the completion of the test, to see how fast the excess of sugar would disappear from the blood stream. It will be noted that our figures for normal tolerance are much higher than those of the originators of the method, which is probably due to the use of isotonic solutions in our work and the insistence on complete relaxation of the animal.

Following various surgical procedures, which were to be tested, such tolerance determinations were repeated once or twice a month, the first determination usually being made two weeks after the operation. All dogs used in this series were observed for at least six months, but some were followed for over two years.

In addition, blood sugar curves were determined following small intravenous injections of epinephrine and insulin before and after the operation. Epinephrine was given in doses of 0.02 mg. per kilogram of weight, and insulin in doses of 0.1 unit per kilogram. The blood sugar was determined at ten, twenty and thirty minutes and one, one and a half and two hours after injection by the modified Folin-Wu method.

The operations performed were: (1) ligation of the tail of the pancreas, which was effected by tying a strong silk ligature or narrow tape of linen around the splenic portion of the gland; (2) adrenal denervation, which was obtained by cutting the splanchnic nerves and small sympathetic branches to the left adrenal gland and removing the right adrenal gland; (3) denervation of the liver, which was obtained by the complete severance of all structures in the liver pedicle with the exception of the hepatic artery, hepatic vein, hepatic duct and portal vein, which were carefully stripped and, in addition, touched with phenol, and (4) celiac ganglionectomy. The left adrenal gland was exposed by an incision running parallel to the left costal margin. The left suprarenal plexus was picked up and followed toward the median line. Above the celiac axis, the left and right semilunar ganglions were exposed and removed, their connections with subordinate plexuses being cut.

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of Ligation of the Tail of the Pancreas on Diastase in the Blood, ibid. **19**:788 (Nov.) 1929. de Takáts, G.; Hennett, F.; Henderson, D., and Seitz, I. J.: IV. The Effect of Isolation of Tail of Pancreas on Carbohydrate Metabolism, ibid. **20**:866 (May) 1930.

4. Woodyatt, R. T.; Sansum, W. D., and Wilder, Russell M.: Prolonged and Accurately Timed Intravenous Injections of Sugar, J. A. M. A. **65**:2067 (Dec. 11) 1915.

RESULTS OF OPERATIONS

Ligation of the Tail of the Pancreas.—In previous communications the suggestion of Mansfeld,[5] that a ligature around the body of the pancreas increases sugar tolerance, was investigated. There is adequate evidence to show that when the tail of the pancreas, which contains more islet tissue than the rest of the gland, is turned into a ductless gland by obstructing the external secretion, hypertrophy and hyperplasia of islet tissue develop in the ligated tail, with a corresponding increase in sugar tolerance. Observations on two diabetic children, on whom such an operation was carried out, confirmed the experimental findings of a rise in tolerance.[6]

It has been assumed by Mansfeld and other workers, who repeated his experiments,[5] that the increase in tolerance was due to a hyperfunction of islets in the tail of the pancreas. While this was unmistakably so a few months after the operation, biopsies undertaken from ten to fifteen months after the operation showed that the excluded portion of the pancreas had almost disappeared, with the exception of the duct and strips of sclerotic tissue around it (fig. 1). This is not surprising in view of the observation made on pancreatic transplants by Ivy and Farrell,[7] that an atrophy and fibrosis of the transplant took place when it was prevented from secreting pancreatic juice. The degree of sclerosis following obstruction of the duct has been carefully studied by Jorns,[8] who stated that a ligature of the duct would be followed by a greater rise in tolerance than a complete severance of the duct, because in the former case the duct would become reestablished and prevent the progressive strangulation of the islets.

In marked contrast to the atrophy of the part distal to the ligature, the unligated part of the pancreas seemed unusually bulky. A section taken from the same dog's pancreas, in which a marked fibrosis was present, distal to the ligature, showed an abundance of islet tissue proximal to the ligature (fig. 2). This compensatory hypertrophy was found in all five dogs that had a ligation of the pancreatic tail from eight to fourteen months previous to exploration. The regenerative power of

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5. Mansfeld, G.: Versuche zu einer operativen Behandlung des Diabetes, Klin. Wchnschr. **6**:1, 1927.

6. (*a*) de Takáts, G., and Wilder, R. M.: Isolation of Tail of Pancreas in a Diabetic Child, J. A. M. A. **93**:606 (Aug. 24) 1929. (*b*) de Takáts, G.: Ligation of the Tail of the Pancreas in Juvenile Diabetes, Endocrinology **14**:255, 1930; The Effect of Ligating the Tail of the Pancreas in Juvenile Diabetes, Surg., Gynec. & Obst. **53**:45 (July) 1931.

7. Ivy, A. C., and Farrell, J. I.: A Method for the Subcutaneous Transplantation of the Tail of the Pancreas, Am. J. Physiol. **77**:474 (July) 1926.

8. Jorns, G.: Experimentelle und klinische Beiträge zur Pathologie der Langerhans'schen Inseln, Beitr. z. klin. Chir. **146**:1, 1929.

the pancreas has been emphasized by F. M. Allen,[9] Fahr [10] and others. Removal of pancreatic tissue, however, results not only in regeneration but in a superregeneration, as manifested by an increase in sugar tolerance [11] unless the gradual removal is carried to a point of exhaustion in the remnant.

When the ligated portion of the pancreas is removed from the dog, which shows an increase in sugar tolerance, the tolerance does not drop, but on the contrary rises (fig. 3). This can be explained only by the stimulating effect of the removal of the tail on the remnant. Thus, we were unable to confirm the statement of Mansfeld,[5] that the removal of
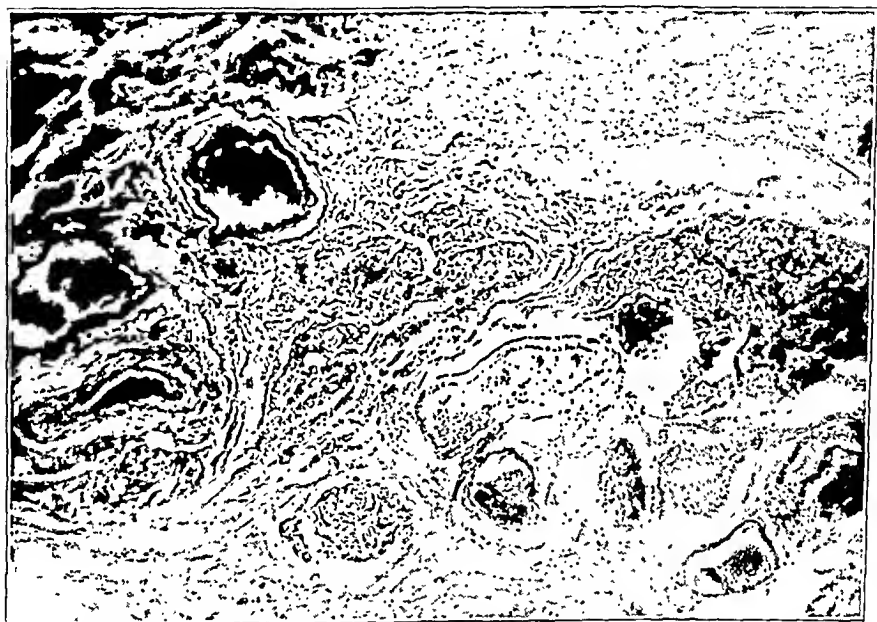
Fig. 1.—Marked sclerosis of the ligated tail of the pancreas, one year after the operation. There are only small patches of parenchyma left. The blood vessels are numerous and have thick walls, indicating the increased resistance of the tissues to blood flow. There are no islets visible in this field. Fibrous connective tissue dominates the picture.

the ligated tail of the pancreas terminates the increased tolerance in the experimental animal.

The rise in tolerance then observed following a massive ligature around the body of the pancreas produces a hypertrophy and hyperplasia

9. Allen, F. M.: Studies Concerning Diabetes and Glycosuria, Boston, W. M. Leonard, 1913.

10. Fahr, T.: Diabetes Studien, Virchows Arch. f. path. Anat. **215**:247, 1914.

11. Elias, M., and Waller, K.: Zur Wiederherstellung der Funktion des Inselapparates, Ztschr. f. d. ges. exper. Med. **74**:81, 1930.

of the islets in the ligated portion; later, however, a progressive sclerosis replaces the destroyed acinar tissue and invades the islands, and a compensatory regeneration and even a hyperregeneration of the unligated portion supervene. As the insular tissue functions according to existing needs, a hyperfunction cannot be expected to persist in the normal animal."

The experience with two diabetic children, in whom the ligation of the tail of the pancreas was performed, indicated an unmistakable improvement of sugar tolerance, but as long as further hypodermic administration of insulin was still necessary the operation did not accomplish its object.

Fig. 2.—Section from the body of the pancreas. The tail was ligated six months previously. There is an abundance of islet tissue. The section looks like many of the pictures obtained from ligated portions, but there is no dilatation of ducts and no increase in fibrous tissue.

Ligation of the Tail of the Pancreas and Adrenal Denervation.—It was reasonable to assume that if an increased or uninhibited secretion of insulin were present following ligation of the tail of the pancreas, the mechanism which normally maintains the blood sugar level would attempt a compensation. The emergency theory of Cannon, McIver and Bliss[12] could be well applied to a prolonged state of hyperinsulinism.

12. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**:46, 1924.

Thus, Riddle [13] in doves and Langecker [14] in rabbits produced an increase in the size and weight of the adrenals following prolonged administration of insulin. In man, Gray and Feemster [15] described a hypertrophy of the suprarenal medulla in the presence of insular hypertrophy and hyperplasia, whereas Chiari [16] reported an insulin-resistant diabetes with a large suprarenal hyperplasia. The patient had received 100 units of insulin without any lowering of blood sugar.

That such a suprarenal response might be at play following the increased activity of islet tissue after ligation of the pancreatic tail was suggested to us by an unmistakable enlargement of the adrenals seen in four of six dogs that came to autopsy not earlier than a year after the
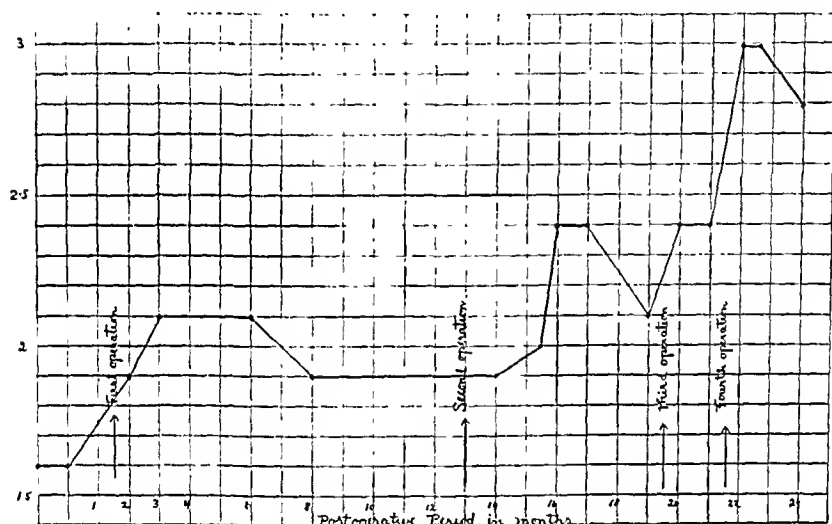
Fig. 3.—Sugar tolerance curve of dog 50 (measured in grams per kilogram per hour). Following ligation of the tail of the pancreas (on March 20, 1930), the tolerance rose from 1.6 Gm. per kilogram per hour to 1.9 Gm., and after three months, to 2.1 Gm. This tolerance was maintained for three months, after which a decline took place. The removal of the ligated tail (on April 23, 1931) did not decrease the tolerance further, but, on the contrary, a second rise took place, reaching the peak of 2.4 Gm. three months after the second operation. When this curve declined, splanchnic section on one side (on September 29) and later on the other side (on November 24) resulted in a steep rise of tolerance, becoming stabilized at 2.8 Gm.

13. Riddle, O.; Honeywell, H. E., and Fisher, W. S.: Suprarenal Enlargement Under Heavy Dosage of Insulin. Am. J. Physiol. **68**:461 (May) 1924.

14. Langecker, Hedwig: Der Einfluss chronischer Insulinzufuhr auf die Nebennieren beim Kaninchen, Arch. f. exper. Path. u. Pharmakol. **134**:155, 1928.

15. Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother, Arch. Path. **1**:348 (March) 1926.

16. Chiari, H.: Ein Fall von Diabetes mit Hypertrophie der Nebennierenrinde, Wien. klin. Wchnschr. **42**:1318 (Oct. 10) 1929.

tail of the pancreas was isolated. In three cases the medulla was cystic and the cortex enlarged. When adrenal denervation was added to ligation of the pancreatic tail, the sugar tolerance rose up to the fourth month, closely corresponding with the rise following the pancreatic operation, but instead of declining after the fifth month, it continued to rise, reached a peak at the sixth month and remained high until the eighth month, the end of the observation (fig. 4). There was no enlargement of the adrenals in this series.

Thus, the second group of experiments seemed to inhibit the medulliadrenal response to the increased activity of the insular apparatus. But in the light of the experiments of Britton and his co-workers,[17] who found that cats became exceedingly sensitive to insulin following inac-
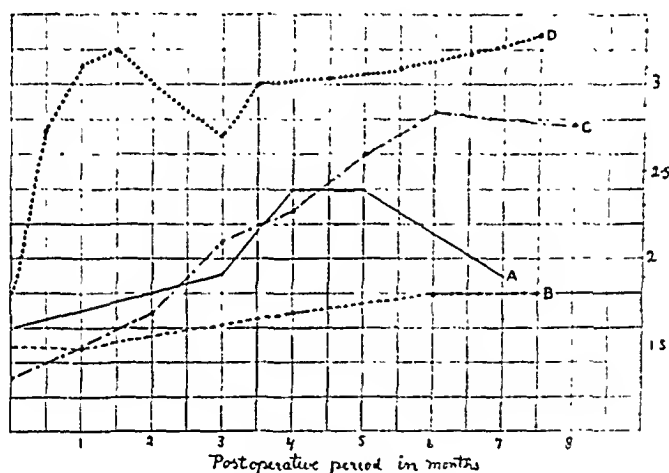
Fig. 4.—Composite graph, indicating the effect of various operations on sugar tolerance (measured in grams of dextrose per kilogram per hour). *A* represents the fluctuations in tolerance following ligation of the tail of the pancreas (in five dogs). A gradual rise, a peak at the fourth month, a decline after five months and a somewhat higher status at seven months than before operation are shown. *B* shows the tolerance after denervation of the liver (two experiments). There was no appreciable rise in tolerance, except that due to a better relaxation of the animal. The tolerance never rose above 2 Gm. per kilogram per hour. These two experiments also serve as controls, to show that repeated intravenous determinations per se do not increase tolerance above the normal level. *C* represents the tolerance curves of five dogs with denervation of the adrenals and ligation of the tail of the pancreas. The rise in tolerance in these dogs showed a gradual character, but around the fifth month, when tolerance declined again in a dog with ligation of the tail alone, the five animals increased their tolerance to almost 3 Gm. per kilogram per hour. *D* illustrates the average of the tolerance curves of five dogs that had undergone celiac ganglionectomy. With the exception of one dog in which the tolerance had not been determined before the fifth month, the tolerance rose suddenly after the operation, in one case reaching the height of 3.8 Gm. per kilogram per hour.

17. Britton, S. W.; Geiling, E. M. K., and Calvery, H. O.: Medulli-Adrenal Secretion and Carbohydrate Metabolism, Am. J. Physiol. **84**:141, 1928.

tivation of the adrenal medulla, adrenal denervation per se must profoundly influence carbohydrate metabolism. Thus the blood sugar curves following the administration of epinephrine and insulin show a sluggish response to the former and a marked hypersensitivity to the latter (fig. 5). In one instance adrenal denervation was claimed to protect a pancreatectomized dog from diabetes.[18]

Denervation of the Liver.—This operation was undertaken with the idea of interrupting all nervous impulses that might lead to a mobilization of glycogen. In 1894, Cavazzani[19] observed that the liver cells lost glycogen and became smaller, and that the blood sugar rose, when the celiac plexus was stimulated with an electric current. Recently, Depisch, Hasenöhrl and Schönbauer[20] reported a flattening of tolerance curves following denervation of the liver pedicle both in normal and in partially pancreatectomized dogs. Soon after we started this series of experiments, Donald's work from Mann's laboratories appeared, which
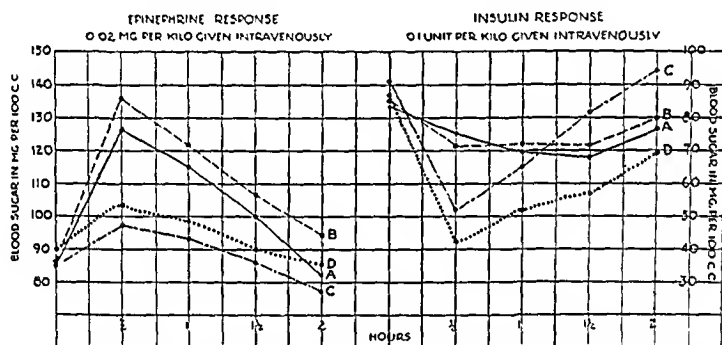
Fig. 5.—Response to epinephrine and insulin following various surgical procedures. Epinephrine was given in doses of 0.02 mg. per kilogram of body weight in 10 cc. of physiologic solution of sodium chloride, intravenously. Insulin was administered intravenously, 0.1 unit per kilogram of body weight. *A* is the average of thirty curves of normal controls. In *B* (average of five curves), note that denervation of the liver did not change the response to epinephrine or insulin. Epinephrine hyperglycemia was diminished in the group that underwent ligation of the pancreatic tail and adrenal denervation (*C*, average of thirty curves). The most striking change in the response to insulin occurred in the dogs with denervated adrenals (*D*, average of ten curves), because not only was the hypoglycemic dip marked but the recovery to a normal level was retarded. The dogs with denervation of the liver behaved like the control animals.

18. Ciminata, H.: Einfluss der Durchschneidung der Nebennieren auf den Diabetes mellitus, Klin. Wchnschr. **11**:150, 1932.

19. Cavazzani, Emil: Ueber die Veränderungen der Leberzellen während der Reizung des Plexus coeliacus. Arch. f. d. ges. Physiol. **57**:181, 1894.

20. Depisch, F.; Hasenöhrl, R., and Schönbauer, L.: Die Durchschneidung der vegetativen Nerven im Ligamentum hepatoduodenale. Klin. Wchnschr. **9**:1437, 1930.

shows conclusively that denervation of the liver does not affect carbohydrate metabolism.[21] Therefore, we contented ourselves with the study of two dogs that had been observed for over seven months and that showed identical results, namely, that denervation of the liver pedicle did not increase sugar tolerance (fig. 4). We have used these two dogs for controls, illustrating that repeated tolerance determinations will not increase the sugar tolerance, at any time, over 2 Gm. of dextrose per kilogram per hour. The response to epinephrine and insulin does not differ from that of the controls (fig. 5).

Celiac Ganglionectomy.—This operation denervates extrinsically the pancreas, the adrenals and the liver. The latter receives some vagal branches from the left side, which may be sectioned separately. The nervous control of carbohydrate metabolism has been emphasized in Claude Bernard's experiments with piqûre. The older literature has been summarized by Mock and one of us (Dr. de Takáts.[22]). The reviews of Pollack [23] and McLeod,[24] together with several experimental studies.[25] indicate (1) that vagal stimulation produces hypoglycemia, presumably through secretion of insulin, and (2) that splanchnic section increases the sensitivity to insulin. The exaggerated response of sympathectomized animals to insulin has recently been investigated by Dworkin.[26]

In the light of these data it seemed important to examine the effect of celiac ganglionectomy on sugar tolerance, as previous data in the literature were absent. The operation was performed on five dogs, and the results were followed over a period of at least seven months (fig. 4). The rise in tolerance has been higher than that observed with any other procedure, in one dog reaching the peak of 3.83 Gm. per kilogram per hour. This change took place immediately after the operation, when

21. Donald, Joseph M.: Studies on Carbohydrate Metabolism of the Liver, Am. J. Physiol. **98**:605 (Nov.) 1931.

22. Mock, Harry E., and de Takáts, G.: Hyperglycemia Following Head Injuries, Ann. Surg. **90**:190 (Aug.) 1929.

23. Pollack, Leo: Pathologie und Physiologie der Blutzuckerregulation, Ergebn. d. inn. Med. u. Kinderh. **23**:337, 1923.

24. McLeod, J. J. R.: Regulation of the Secretion of Insulin, Lancet **2**:512, 1931.

25. Rupp, W.: Ueber den Einfluss des Nervensystems auf den Zuckergehalt · des Blutes, Ztschr. f. d. ges. exper. Med. **44**:476, 1925. Britton, S. W.: The Nervous Control of Insulin Secretion, Am. J. Physiol. **74**:291, 1925. Clark, G. A.: The Influence of the Vagus on the Islets of Langerhans, J. Physiol. **59**:466, 1925. Geiger, E., and Szirtes, F.: Maximale Hypoglykemie ohne Insulin, Arch. f. exper. Path. u. Pharmakol. **119**:1, 1927. Dresel, K., and Omonsky, F.: Der Einfluss des Vagus- und der Splanchnicusdurchschneidung auf die Adrenalinhyper- und die Insulinhypoglykämie, Ztschr. f. d. ges. exper. Med. **53**:371, 1927.

26. Dworkin, S.: The Response of Sympathectomized Animals to Insulin, Am. J. Physiol. **98**:461 (Oct.) 1931.

the dogs had sufficiently recovered
the contrary seems to be slowly
markedly exaggerated (fig. 6). Wh..
the completion of the intravenous
hours afterward, the low peak, at th
hypoglycemic level at one hour are
dog (fig. 7).

Fig. 6.—Response to insulin following celiac ganglionectomy. The normal, pre-operative response is indicated by the interrupted line. The straight lines indicate the response to insulin in three dogs following operation. Note the maximal dip in from ten to twenty minutes, which reached the value of 41 mg. of dextrose following the intravenous administration of 0.1 unit of insulin per kilogram of body weight. The blood sugar is measured in milligrams per hundred cubic centimeters.

Fig. 7.—Blood sugar determinations before, at the completion of, and for several hours following, the intravenous administration of 5 per cent dextrose at the rate of 2 Gm. per kilogram per hour. The straight lines indicate the normal control (a dog, weighing 17 Kg.); the interrupted line, a dog weighing 20 Kg., in which the celiac ganglion was removed five months previously.

The dogs in all four series maintained excellent health and did not lose weight. Their tolerance was occasionally influenced by skin or respiratory infections. In only one dog in the last series did diarrhea and a progressive loss of weight develop. He was excluded from further observation.

COMMENT

It seems, then, from the foregoing data that sugar tolerance in the normal dog, as determined with intravenous injections of dextrose at timed rates, may be raised by various surgical procedures. The rise in tolerance that follows the ligation of the tail of the pancreas comes on gradually, reaches its peak from the third to the sixth month following operation and later declines. The atrophy of the ligated tail produces a superregeneration of the unligated portion which may be accentuated by a secondary removal of the ligated part. Like all processes of repair, the superregeneration does not progress or remain unchanged, but gradually adapts itself to the functional needs of the normal body. Our observations on diabetic children with this method would not indicate, outside of a decided increase in tolerance, that the original diabetogenic factor had been excluded. This was pointed out in our first communication with Wilder.[6a]

If, however, the point of attack is the nervous regulation of carbohydrate metabolism, the most rapid and greatest increase in tolerance is accomplished by celiac ganglionectomy. The tolerance rises rapidly and is maintained at the average level of 3.4 Gm. per kilogram at the eighth month, although an individual rise of 3.8 Gm. has been recorded, and one dog showed a tolerance of 3.6 Gm. at the end of one year. This means that a dog weighing 15 Kg. would utilize, instead of 30 Gm. of dextrose given intravenously, an amount of 51 Gm., a hitherto unobserved rise in tolerance.

The explanation of this large rise in tolerance cannot yet be attempted. As denervation of the liver has no effect on sugar tolerance, there remains the effect of denervation on the pancreas and adrenals. That the inactivation of the adrenals increases insulin susceptibility has been shown without doubt, and our own observations confirm this. As to the effect of celiac ganglionectomy on the pancreas, an increased flow of blood or an inhibition of vasoconstrictor impulses to the vascular system of the islets could be thought of. This operation also inhibits the enzyme secretion of the pancreas.[27] If it could be shown that the rise in tolerance is not entirely lost in the absence of the pancreas, this would focus the entire problem on the adrenals.

If these experiments on the nervous control of carbohydrate metabolism are to have a clinical application, they would have to be based on the acceptance of the "overproduction" theory of diabetes, with a denial of impairment in carbohydrate oxydation by the diabetic organism. The work of Soskin[28] has furnished significant data in this direction.

27. Baxter, S. G.: Nervous Control of the Pancreatic Secretion of the Rabbit, Am. J. Physiol. **96**:349, 1931.

28. Soskin, S.: The Utilization of Carbohydrate by Totally Depancreatinized Dogs Receiving No Insulin, J. Nutrition **3**:99 (Sept.) 1930.

SUMMARY

Four series of experiments have been conducted with the object of increasing sugar tolerance in the normal dog: (1) ligation of the tail of the pancreas, (2) ligation of the tail of the pancreas with denervation of the adrenals, (3) denervation of the liver and (4) celiac ganglionectomy. The first procedure laid stress on an increased or uninhibited output of insulin, which does not persist in the normal animal indefinitely. When adrenal denervation is added, however, to the first operation, the tolerance is maintained on a high level. Denervation of the liver did not affect sugar tolerance. Celiac ganglionectomy raised the sugar tolerance to hitherto unobserved levels, and its effect has lasted as long as fourteen months unchanged.

Tests for epinephrine and insulin susceptibility showed that liver denervation did not alter the normal response to either of these hormones. However, adrenal denervation and celiac ganglionectomy flattened the epinephrine-glycemia curves and markedly increased the insulin hypoglycemia. These tests indicate the profound influence of these operations on carbohydrate metabolism.

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ABSTRACT OF DISCUSSION

DR. JOSEPH A. DANNA, New Orleans: I have followed with considerable interest reports in the recent literature of surgical removal of adenomas and other tumors of the pancreas which were giving rise to clinical pictures suggestive of hyperinsulinism. The successful results in a number of these cases have helped to place the pancreas, or at least the island tissue of the pancreas, in the group of glands like the thyroid, pituitary, parathyroid, etc., in that it is capable of hyperfunction as well as hypofunction. The surgical results in a number of cases of hyperinsulinism have corresponded with the results obtained in thyroidectomy, operations on the pituitary and parathyroid glands, etc. We seemed to be quite helpless, however, in influencing the course of diabetes or hypo-insulinism by any surgical procedure.

The wonderful results following sympathectomy in Raynaud's disease, Buerger's disease and even angina pectoris are familiar to all of us. It remained for Dr. de Takáts, however, to conceive the possibility of attacking the organs concerned with sugar metabolism through the removal of their sympathetic control. The results which he reports are remarkable. It only remains now to see how well a human being will stand the removal of the semilunar ganglions. I was reminded by Dr. de Takáts' experiments in denervation of the adrenal gland of the work of Dr. George Crile, who, I believe, has done more denervations of suprarenals in human beings than any one else. I was anxious to know whether he noted the same changes in blood sugar and sugar tolerance as took place in Dr. de Takáts' animals. I had hoped that Dr. Crile would be here to relate his own experience in this regard, but when I found that he was not coming, I wired him and received from him this answer: "Adrenal denervation increases sugar tolerance and lowers blood sugar. In a limited number of cases of operations on diabetic patients they have been greatly improved and may prove to be cured."

This I interpret as fully corroborative of Dr. de Takáts' work. I have not had any experience in the removal of the great splanchnic ganglions in the human being. Their comparative surgical inaccessibility will probably not encourage many of us, especially in the presence of so serious a condition as diabetes, to make the attempt.

I have been wondering as to the feasibility of performing the Leriche operation on the splenic artery and on the gastroduodenal arteries, separating the pancreas from its bed and tucking a layer of omentum between it and its bed. This itself would be a formidable and difficult procedure, and the very free arterial and hence, probably, sympathetic anastomoses and the difficulty of entirely isolating the pancreas would not promise much hope of marked lasting results. I shall look to the near future with considerable interest for further developments in this fascinating field, and especially to the results of the activity and further investigation of Dr. de Takáts.

Dr. J. Shirley Sweeney, Dallas, Texas: This interesting paper contains many promising implications. Dr. de Takáts has demonstrated something by his research that we cannot explain. To the internists he has raised some controversial points.

When we stop to remember that the cause of diabetes mellitus is unknown, it is easy to understand why there may exist different theories as to the pathologic physiology of the disorder. Dr. de Takáts refers to the overproduction theory of diabetes mellitus, stating: "If these experiments on the nervous control of carbohydrate metabolism are to have a clinical application, they would have to be based on the acceptance of the overproduction theory of diabetes, with a denial of impairment in carbohydrate oxidation by the diabetic organism," and at this point he refers to the experiments of Soskin as furnishing significant data in this direction. I wish that he would make this statement a little clearer. I think that in some of Soskin's depancreatized dogs there was evidence of active sugar metabolism as well as fat metabolism. Furthermore, I have always felt that fat metabolism was dependent on sugar metabolism. If the continued metabolism of sugar and fat might be ascribed to extrapancreatic insulin, the paradox might be explained, but since Best and his co-workers have recently proved there is no insulin except in the pancreas, we are in doubt again.

It is difficult for me to give up the idea that a deficiency of insulin is the reason for diabetes. It seems to me so much more physiologic than the concept of gluconeogenesis—a hypothetic process. Conversely, certainly when excessive insulin is produced, as in metastastizing carcinoma of islet tissue, we have the antithesis of diabetes mellitus. But neither time nor an audience, composed largely of surgeons, permits a technical discussion of this phase of the subject. In the ligation operation, nervous control was undisturbed and an increase in sugar tolerance resulted, presumably owing to a regeneration of islet structures or more insulin. This seemed to be true also in the cases in human beings described by Dr. de Takáts in other communications. True, the tolerance increased more following celiac ganglionectomy, but why is it not the same process, possibly by either blocking an inhibiting influence or by increasing pancreatic blood supply or diminishing adrenal secretion—a neutralizing substance?

The recent observations of Zimmerman and Soskin are noteworthy. They found that by ligating the parotid ducts of normal dogs they were able to increase sugar tolerance, whereas in depancreatized dogs the same operation produced no results.

There is an inextricable relation between sugar and fat metabolism. This is noted, especially in diabetes mellitus in adults, by the almost invariable antecedent obesity. Something, it seems, happens to fat metabolism and then to sugar metab-

SUMMARY

Four series of experiments have been conducted with the object of increasing sugar tolerance in the normal dog: (1) ligation of the tail of the pancreas, (2) ligation of the tail of the pancreas with denervation of the adrenals, (3) denervation of the liver and (4) celiac ganglionectomy. The first procedure laid stress on an increased or uninhibited output of insulin, which does not persist in the normal animal indefinitely. When adrenal denervation is added, however, to the first operation, the tolerance is maintained on a high level. Denervation of the liver did not affect sugar tolerance. Celiac ganglionectomy raised the sugar tolerance to hitherto unobserved levels, and its effect has lasted as long as fourteen months unchanged.

Tests for epinephrine and insulin susceptibility showed that liver denervation did not alter the normal response to either of these hormones. However, adrenal denervation and celiac ganglionectomy flattened the epinephrine-glycemia curves and markedly increased the insulin hypoglycemia. These tests indicate the profound influence of these operations on carbohydrate metabolism.

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ABSTRACT OF DISCUSSION

DR. JOSEPH A. DANNA, New Orleans: I have followed with considerable interest reports in the recent literature of surgical removal of adenomas and other tumors of the pancreas which were giving rise to clinical pictures suggestive of hyperinsulinism. The successful results in a number of these cases have helped to place the pancreas, or at least the island tissue of the pancreas, in the group of glands like the thyroid, pituitary, parathyroid, etc., in that it is capable of hyperfunction as well as hypofunction. The surgical results in a number of cases of hyperinsulinism have corresponded with the results obtained in thyroidectomy, operations on the pituitary and parathyroid glands, etc. We seemed to be quite helpless, however, in influencing the course of diabetes or hypo-insulinism by any surgical procedure.

The wonderful results following sympathectomy in Raynaud's disease, Buerger's disease and even angina pectoris are familiar to all of us. It remained for Dr. de Takáts, however, to conceive the possibility of attacking the organs concerned with sugar metabolism through the removal of their sympathetic control. The results which he reports are remarkable. It only remains now to see how well a human being will stand the removal of the semilunar ganglions. I was reminded by Dr. de Takáts' experiments in denervation of the adrenal gland of the work of Dr. George Crile, who, I believe, has done more denervations of suprarenals in human beings than any one else. I was anxious to know whether he noted the same changes in blood sugar and sugar tolerance as took place in Dr. de Takáts' animals. I had hoped that Dr. Crile would be here to relate his own experience in this regard, but when I found that he was not coming, I wired him and received from him this answer: "Adrenal denervation increases sugar tolerance and lowers blood sugar. In a limited number of cases of operations on diabetic patients they have been greatly improved and may prove to be cured."

Dr. Géza de Takáts, Chicago: The effect of the removal of semilunar ganglions in the normal dog has been carefully studied. These dogs maintain perfect health. They do not gain or lose weight. Occasionally there is an increased peristalsis with a diarrhea for a number of weeks, which, however, always adjusts itself. So far as I know, studies of the effect of celiac ganglionectomy performed for other reasons in human subjects have not been made. I do know, however, of patients who have had the splanchnic nerves cut, and in such cases there is an increased peristalsis for a few weeks.

Suprarenal denervation, of course, can be accomplished not only by Dr. Crile's technic but by bilateral splanchnic section, which seems to me a simpler procedure.

Regarding the remark of Dr. Sweeney, Soskin reported on totally depancreatized dogs which still utilized carbohydrates. Therefore his work would confirm the old conception that in diabetes the primary disturbance is an overproduction of sugar and that the insulin deficiency is secondary, resulting from exhaustion of the islets.

So far as diabetes in human beings is concerned, these experiments do not and cannot settle the etiology of diabetes, but it would seem that diabetes is not a uniform disease, that persistent hyperglycemia and glycosuria are a symptom. There must be a true pancreatic diabetes following, for instance, an acute pancreatic necrosis. There may be, perhaps, a neurogenic diabetes, the existence of which is denied by many.

Regarding the operations on the two diabetic children that Dr. Harris referred to, both patients showed a very beneficial effect in that sugar tolerance was stabilized. However, I have felt from the beginning that all we accomplished was to raise their sugar tolerance, and that they are taking now less insulin and perhaps a little more carbohydrate. It is with this idea in mind that we have undertaken the study of the nervous regulation of carbohydrate metabolism with the ultimate hope of attacking certain types of diabetes from this angle.

CARDIAC INNERVATION

EXPERIMENTAL AND CLINICAL STUDIES

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The late Sir James Mackenzie is reputed to have said that discussions on angina pectoris are usually futile, as they simply consist of the replacement of one speculative hypothesis by another. This has been true both as to the etiology of the disease and as to the most logical surgical method of preventing the attacks. It is not within the scope of this paper to review the multitudinous theories which have been put forward to explain the cause of these painful crises; suffice it to say that by their very number Mackenzie's dictum has remained substantiated for many years. Recently, however, an increasing number of cardiologists have subscribed to the theory of Keefer and Resnik,[1] that most cases of angina pectoris can be accounted for on the basis of anoxemia of the myocardium. The experiments of Sutton and Lueth [2] have given strong support to this theory of the etiology of cardiac pain, as they have shown in dogs that interruption of the flow of blood in a coronary artery causes an immediate and unmistakable pain response.

As concerns the second point at issue, there has been no unanimity of opinion concerning the best operative approach to the problem. In the most up to date review of cardiac surgery, Cutler [3] stated that little is known with any certainty about the nerve pathways concerned in angina pectoris. The reason for this present uncertainty is due to the number of operations which have been advocated and to· the fact that all have given good results in some cases and complete failures in others. The reader who wishes to familiarize himself with these different procedures is referred to the writings of Jonnesco,[4] Leriche,[5]

From the Surgical Services of the Massachusetts General Hospital.

1. Keefer, C. S., and Resnik, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, Arch. Int. Med. **41**:769 (June) 1928.

2. Sutton, D. C., and Lueth, H. C.: Pain, Arch. Int. Med. **45**:827 (June) 1930.

3. Cutler, E. C.: The Present Status of Cardiac Surgery, Surg., Gynec. & Obst. **54**:274, 1932.

4. Jonnesco, T.: Traitement chirurgical de l'angine de poitrine par la résection du sympathique cervico-thoracique, Bull. Acad. de méd., Paris **84**:93, 1920.

5. Leriche, R., and Fontaine, R.: The Surgical Treatment of Angina Pectoris, Heart **3**:649, 1928.

Danielopolu,[6] Hofer,[7] Coffey and Brown,[8] Richardson and White[9] and many others. Reid and Andrus[10] have reviewed the older operative procedures, and Swetlow[11] and White[12] the newer statistics of paravertebral injections of alcohol. The results of all operative methods are summarized in table 1, which is made up of statistics from the literature compiled by Cutler[13] and Fontaine,[14] with the addition of the reports of operations performed in the Massachusetts General Hospital.

The results of a five year study of this problem have convinced one of us (Dr. White) that the underlying factor which accounts for the unsatisfactory results following the cervical operations is the failure to interrupt enough of the essential nerve connections of the heart. As in many past problems, the possibility of reproducing a condition in animals has helped in the clinical solution. Sutton and Lueth's[2] method of producing cardiac pain by occluding the flow of blood in a coronary

TABLE 1.—*Surgical Procedures in Angina Pectoris*

| | Upper Cervical Sympathectomies | | | Complete Cervical Sympathectomies | | | Thoracic Sympathectomies |
	Fontaine	Cutler*	M.G.H.†	Fontaine	Cutler*	M.G.H.†	M.G.H.†
Number of cases........	57	53	8	37	27	2	4
Results:							
Good...............	66.6%	41.5%	37.5%	56.8%	52%	50%	100%
Improved..........	12.3%	35.8%	......	10.8%	18.5%	....	.....
Failures...........	5.3%	11.2%	50%	8.1%	7.5%	....	.....
Uncertain..........	5.3%	4%	......	5.4%	......	....	.....
Deaths (within 4 days of operation)........	10.5%	7.5%	12.5%	18.9%	22%	50%	0

* Cutler's figures for mortality have been corrected to include deaths occurring within the first four days after operation.
† Massachusetts General Hospital.

6. Danielopolu, D.: L'angine de poitrine et l'angine abdominale, Paris, Masson & Cie, 1927.

7. Hofer, G.: Zur Chirurgie des vegetativen Nervensystems bei Angina pectoris, Wien. med. Wchnschr. **75**:1781 and 2441, 1925.

8. Coffey, W. B., and Brown, P. K.: The Surgical Treatment of Angina Pectoris, Arch. Int. Med. **31**:200 (Feb.) 1923.

9. Richardson, E. P., and White, P. D.: Sympathectomy in the Treatment of Angina Pectoris, Am. J. M. Sc. **177**:161, 1929.

10. Reid, M. R., and Andrus, W. De W.: The Surgical Treatment of Angina Pectoris, Ann. Surg. **81**:591, 1925.

11. Swetlow, G. I.: Paravertebral Alcohol Block in Cardiac Pain, Heart **1**:393, 1926.

12. White, J. C.: Angina Pectoris: Relief of Pain by Paravertebral Alcohol Block of the Upper Dorsal Sympathetic Rami, Arch. Neurol. & Psychiat. **22**:302 (Aug.) 1929.

13. Cutler, E. C.: Summary of Experience Up to Date in the Surgical Treatment of Angina Pectoris, Am. J. M. Sc. **173**:613, 1927.

14. Fontaine, R.: Les résultats actuels du traitement chirurgical de l'angine de poitrine, Thèse de Strasbourg, 1925.

artery has enabled us to find out what operative procedures are necessary for complete interruption of all the cardiac pain tracts. A second experimental procedure of our own has given us further insight into the efferent motor pathways. We propose in this paper to give the results of these experiments and to correlate these findings with our operative experiences.

EXPERIMENTAL METHODS FOR DETERMINING THE CARDIAC PAIN PATHWAYS

The method described by Sutton and Lueth [2] has been used in these experiments for the production of cardiac pain. The animals used were large young dogs, weighing from 10 to 23 Kg. Operation was performed under ether anesthesia, which was administered by insufflation through a catheter inserted in the lower part of the trachea. This method maintained adequate ventilation and distention of the lungs in the presence of open pneumothorax. The fourth rib was resected from the sternum to the midaxillary line and the pleura opened. The pericardium was then drawn up and an incision, 1 inch (2.54 cm.) long, made in it. This gave a good exposure of the tip of the left auricle with the upper portion of the left ventricle and the left part of the right ventricle. The left coronary artery could be seen appearing from under the auricular appendage. It is at this point that it splits into its circumflex and descending branches. The descending branch running downward over the interventricular septum is easily accessible in its upper portion. A fine silk ligature threaded on a curved needle was passed just beneath the uppermost portion of the descending branch of the left coronary artery and its accompanying veins (fig. 1). This was brought out through a glass tube with a flange at its lower end. The pericardium was then tightly closed around the flanged end of the tube, and the wall of the chest sutured in several layers around it to obtain an air-tight closure. Following aspiration of air from the pleural cavity the tracheal catheter was withdrawn and the animal allowed to recover from ether.

These animals seemed to suffer from no shock, and recovered rapidly from their anesthesia. Within an hour to an hour and a half they were up and walking around the laboratory as though little had happened. This procedure was carried out on four control dogs and on seventeen others following varied types of neurosurgical operations to test the presence or absence of conduction of pain. When the cardiac pain fibers were uncut, traction on the ligature for a period of only a few seconds invariably produced a characteristic stiffening of the limbs, a marked increase in the rate and depth of respiration, and if maintained for over ten or fifteen seconds a definite restlessness on the part of the animal. During the tests the dogs were allowed to lie on a large table without any form of restraint. Traction on the thread occluding the coronary artery was never maintained to the point at which the animal showed signs of even moderately severe pain, but was discontinued as soon as the dog appeared to be uncomfortable enough to shift his position. When the pull was released, the animals immediately settled down again in perfectly comfortable attitudes and resumed their normal, regular respiration. Respiration was recorded in each case on a kymograph registering the respiratory movements by means of a small band around the thorax which pulled out a rubber membrane on a small tambour each time the animal inspired. This tambour was connected through rubber tubing with a second tambour recording each inspiration by a downward stroke on the smoked paper. The respiratory tracing appeared to be

the best graphic method of recording painful stimuli. In one case a blood pressure tracing was made as well, but failed to show striking changes when the coronary circulation was occluded.

For want of a better word to describe the characteristic reaction to coronary occlusion, the phenomena described will be referred to hereafter as evidence of cardiac pain. It is most important, however, to emphasize that none of these animals was ever permitted to suffer acutely.

OBSERVATION

1. *Control Observations.*—Four dogs were tested by this method, and three of their respiratory tracings are reproduced in figure 2.
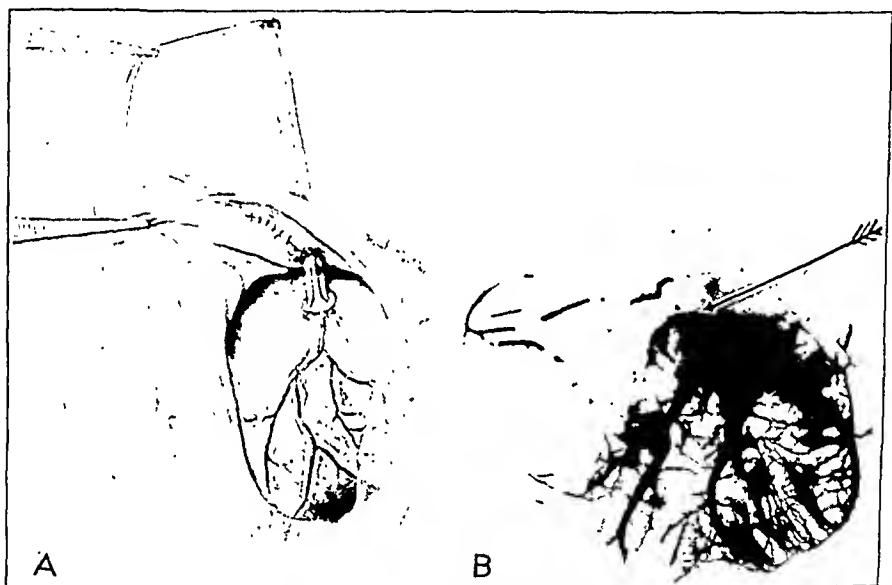
Fig. 1.—*A*, technic for temporary occlusion of descending branch of left coronary artery. *B*, roentgenogram after injection of metallic mercury at the point of constriction (arrow) in the left coronary artery shown in *A*. The blood supply of the entire anterior wall of the left ventricle, part of the right ventricle and the apex of the heart can be temporarily cut off by traction on the ligature.

These curves show strikingly the onset of deep, irregular respiration following occlusion of the descending branch of the left coronary artery. There is a striking contrast between this and the normal regular respiration seen before traction on the ligature and recurring a few seconds after its release. The behavior of these was equally striking and showed a characteristic change from a perfectly comfortable, relaxed animal to one with rapidly increasing discomfort. It was perfectly obvious that if the traction had been maintained a few seconds longer the dogs would have been suffering as acutely as persons in typical attacks of angina pectoris. The straightening and stiffening of the forelegs and

body were also suggestive of a person in an abrupt attack of angina pectoris or coronary occlusion. In each case the attack passed off within a few seconds of the release of tension on the ligature, and the dog again appeared to be perfectly comfortable and ready to rest quietly on the table.

2. *Effect of Left Stellate Ganglionectomy.*—Figure 3 shows the anatomic relationships between the vagus and sympathetic trunks in the dog. In the neck, just below the superior cervical sympathetic ganglion, these two structures combine and form a common vagosympathetic trunk. In the region of the middle cervical sympathetic ganglion the sympathetic again leaves the vagus nerve and passes as the annulus of Vieussens in front of and behind the subclavian artery. These two branches then unite to form the cervicodorsal or stellate ganglion, which in the
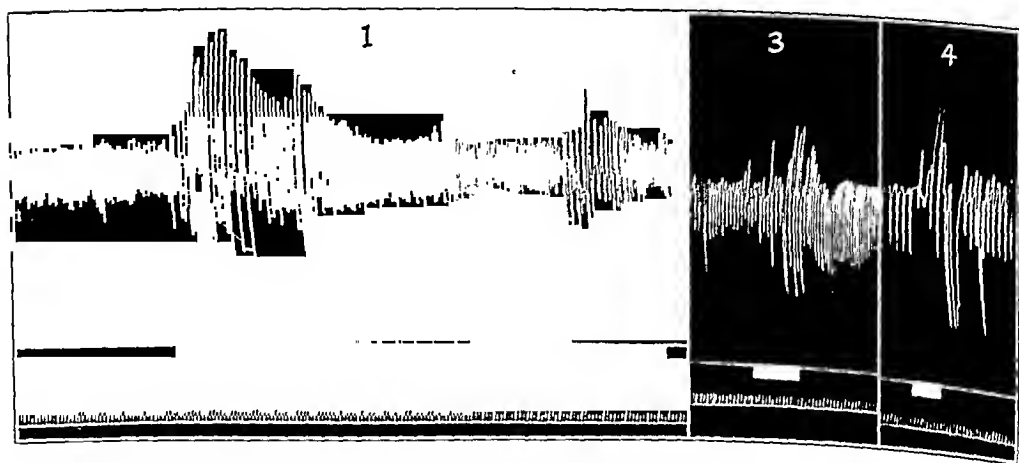
Fig. 2.—Respiratory movements in control dogs, showing response to periods of coronary occlusion of from ten to thirty seconds' duration. In this and each of the subsequent figures, the time intervals are marked in seconds and the duration of coronary occlusion by the broad white signal line.

dog is a fusion of the inferior cervical and first thoracic sympathetic ganglions. It is a large and most important structure, the origin of the inferior cardiac nerve and the first ganglion to receive a white communicant ramus, which means that it is the highest that is connected directly with the spinal cord. The superior and middle cervical sympathetic ganglions, on the other hand, are connected to the spinal cord only by nerve fibers which pass through the stellate ganglion. Below this ganglion the sympathetic trunk becomes considerably smaller. The lower ganglions correspond with each of the intercostal nerves and are connected to them by both white and gray rami.

While the classic sympathetic peripheral pathways run from the cervical and stellate ganglions to the heart. it is possible to see fine

postganglionic fibers leaving the upper two to four thoracic ganglions and running in the direction of the cardiac and pulmonary plexuses. Jonnesco and Enarchesco,[15] Braeucker[16] and Kuntz and Morehouse[17] have recently traced these fibers into the posterior cardiac plexus. Do these fibers carry important pain or motor stimuli which play an important part in angina pectoris? If so, it is obvious that in the human
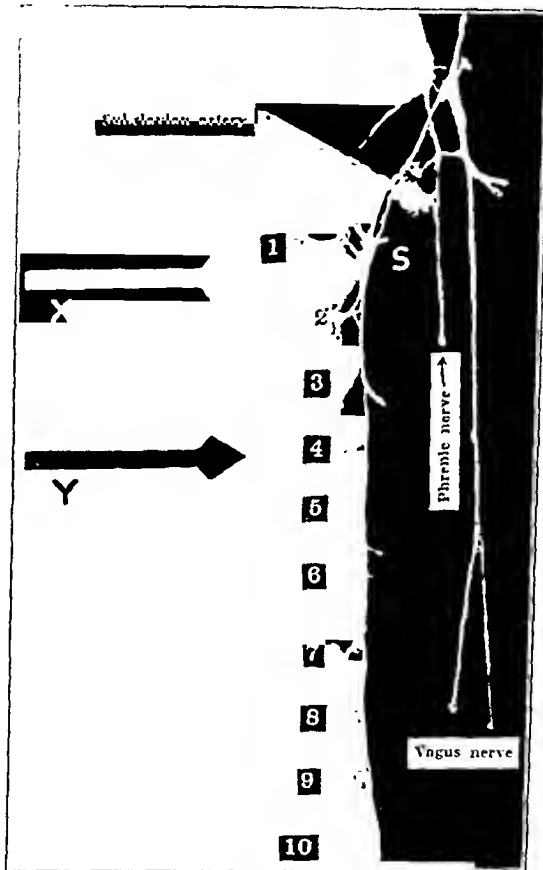
Fig. 3.—Photograph showing the thoracic sympathetic ganglions, the combined vagosympathetic trunk and the thoracic portion of the vagus nerve in the dog. The cervicothoracic or stellate ganglion is marked *S*. The other ganglions are numbered. When the sympathetic trunk is resected between the subclavian artery and the point *X*, cardiac pain is not interrupted. When the resections are carried to the point *Y* on both sides, cardiac sensation appears to be entirely lost.

15. Jonnesco, D., and Enarchesco, M.: Nerfs cardiaques naissant de la chaîne thoracique du sympathique au dessous du ganglion stellaire, Compt. rend. Soc. de biol. 97:977, 1927.

16. Braeucker, W.: Der Brustteil des vegetativen Nervensystems und seine klinische chirurgische Bedeutung, Beitr. z. Klin. d. Tuberk. 66:1, 1927.

17. Kuntz, A., and Morehouse, A.: Thoracic Sympathetic Cardiac Nerves in Man, Arch. Surg. 20:607 (April) 1930.

being no operation performed through the neck can safely reach below the lower part of the stellate ganglion ; hence the presence of these lower structures may well account for the persistence of anginal attacks after cervical sympathectomy.

Figure 4 shows that after unilateral removal of the stellate ganglion, dogs tested by temporary occlusion of the descending branch of the left coronary artery gave distinct, painful responses. This, needless to say, shows that insufficient cardiac pain fibers had been interrupted.

3. *Unilateral Resection of Stellate and Upper Thoracic Ganglions.*— These dogs were subjected to the operation on the sympathetic ganglions from two to seven days previously. The operation was performed
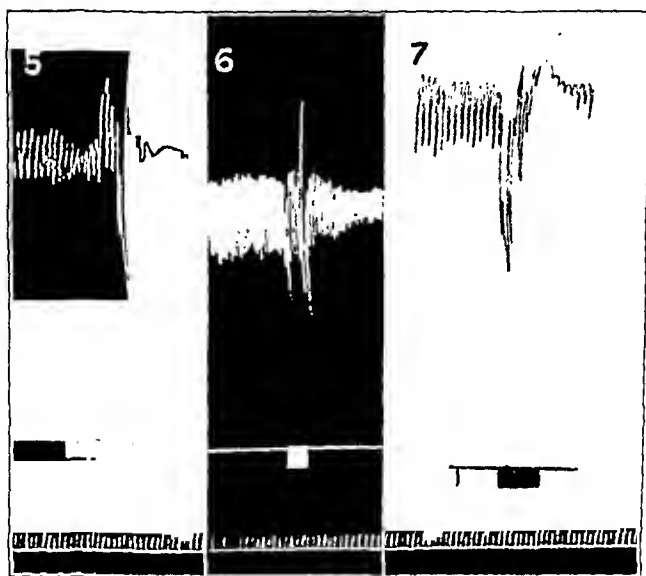
Fig. 4.—Cardiac pain transmission remained intact after resection of the left stellate ganglion in dog 5, the left stellate ganglion through the fourth thoracic ganglion in dog 6 and the left stellate ganglion through the fifth thoracic ganglion in dog 7.

under ether or pentobarbital sodium anesthesia. An incision was made high in the axilla. The pectoralis major and minor and the scaleni muscles were retracted forward. (The scaleni in the dog originate from the lateral surfaces of the upper four ribs as a broad ribbon of muscle.) This gave an excellent exposure of the upper ribs at their vertebral articulations. A 2 cm. section of the proximal portion of the second rib was then removed extrapleurally and the pleura pushed forward off the longus colli muscle. Through this approach the lower portion of the stellate ganglion can be picked up readily, and on cutting its rami the entire ganglion can be removed, along with the fibers of the annulus

of Vieussens up to the subclavian artery. By taking out a short section
of the third or fourth ribs as well, the whole sympathetic trunk down
to the fourth or fifth dorsal ganglions can be removed in one piece.
This procedure can usually be carried out extrapleurally, but even if
the pleura is opened, the dogs tolerate it well, provided the lungs are
kept distended by blowing air down the trachea. When the scalenus
muscle is sutured back in position, the leakage of air into the pleural
cavity is stopped and the residual air can easily be removed by aspira-
tion. This exposure gives an excellent view of the stellate ganglion
and is particularly suited for careful dissection of the ganglions below.
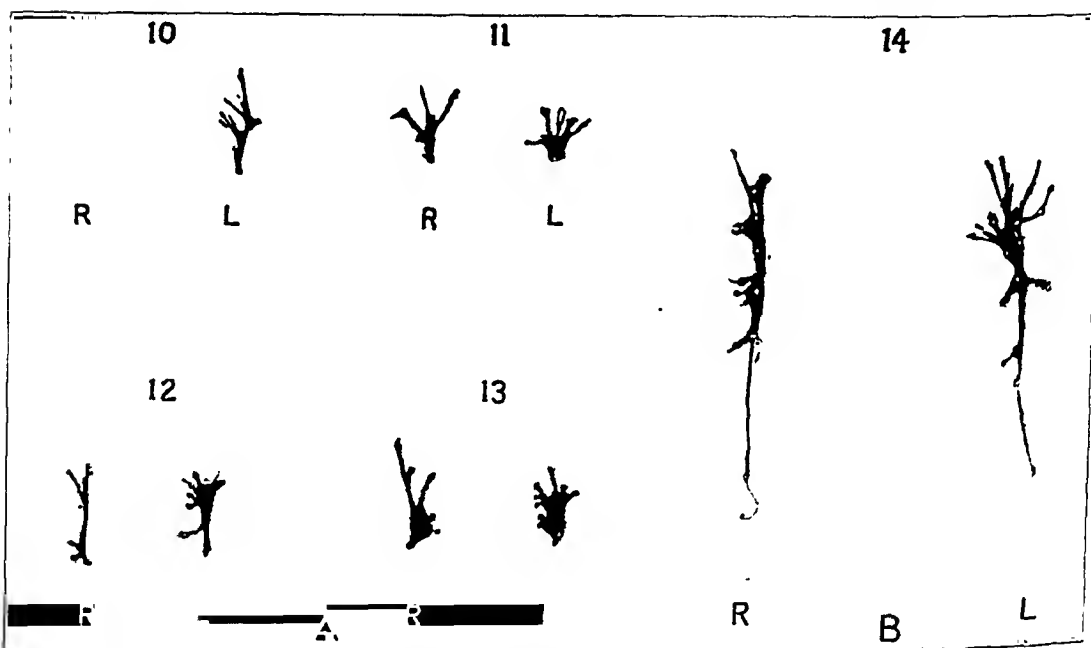
Fig. 5.—Ganglions resected in operations for angina pectoris: *A*, specimens
from bilateral stellate ganglionectomy, the Jonnesco type of operation. Pain could
still be elicited in five of six dogs. The specimen of the right stellate ganglion
in dog 10 was lost. *B*, photograph of specimens after bilateral removal from the
stellate ganglions down through the fourth thoracic ganglions. No pain could be
elicited following this procedure.

After this procedure the operative incisions healed well, and the
dogs were in perfect condition a few days later, when the pain responses
were determined. Figure 4 (dogs 6 and 7) shows that even after
such a radical procedure as unilateral removal of the stellate and upper
four to five thoracic ganglions, cardiac sensation is still intact, although
—as will be seen—it is probably limited to the side not operated on.

4. *Bilateral Stellate Ganglionectomy.*—This procedure amounts to
the Jonnesco operation, as in carrying the dissection upward to the sub-
clavian artery, all the sympathetic connections below the middle cervical

ganglion were removed. Figure 5 shows the extent of the resected nerves. Great care was taken not to injure the sympathetic trunk further down than its first dorsal ramus. By leaving the second dorsal ramus communicans intact, we were taking out as much as could be ordinarily reached through a cervical incision. In fact, it is a question whether more than the inferior cervical portion of the stellate ganglion is usually removed in this operation, as the operators frequently describe the excision of only a single ganglion, and the structure in man normally consists of two separate ganglions with an intervening isthmus. Figure 6 shows that five of six dogs gave distinct painful responses. Dog 11 showed no evidence of pain in his respiratory tracing, but to one observing his behavior it was obvious that he became somewhat restless at the time of stimulation. From these observations it is apparent that
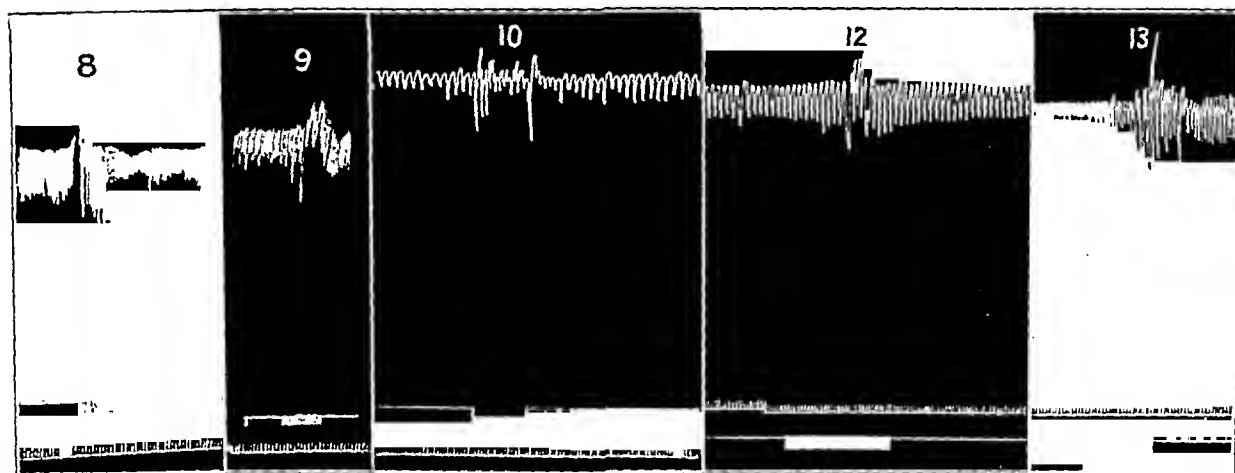
Fig. 6.—Respiratory tracings made following bilateral resection of stellate ganglions. They give clearcut evidence that cardiac sensation is still intact.

pain pathways exist after the complete removal of the lower cervical sympathetic and stellate ganglions on both sides. Do these pathways enter the lower thoracic ganglions through direct postganglionic connections with the heart, or do they reach the central nervous system through the vagus or by still other pathways? We hope to show by the following experiment that it is the recently discovered thoracic cardiac nerves which carry these residual painful stimuli.

5. *Bilateral Resection of Stellate and Upper Four Thoracic Ganglions.*—This operation was carried out in two stages (eight days apart) on an unusually irritable and sensitive young dog. Three days later the usual ligature was passed around the uppermost portion of the descending branch of the left coronary artery. Two hours after operation the dog was completely out of the ether anesthesia, walking

around the laboratory and interested in everything that was going on. On account of his playfulness, it was only with considerable difficulty that he could be induced to lie down and breathe regularly enough to produce an even kymographic tracing. Each time the coronary artery was occluded there was no sign of a response, either in the respiration or in the behavior of the dog (fig. 7). That he was extremely responsive to ordinary stimuli is shown at points in the tracing marked *B*, where the skin of the extremities was lightly pinched. This procedure bears out the results obtained by removal of these ganglions in the human being. One of us (Dr. White [18]) has reported the results of this operation on four human beings. In three of these there has been complete relief of pain on the side operated on, although anginal attacks remain unaltered on the other side. In the one case in which pain has persisted, it is present in a mild form and only over a small area in the arm. This is probably due to the fact that the stellate
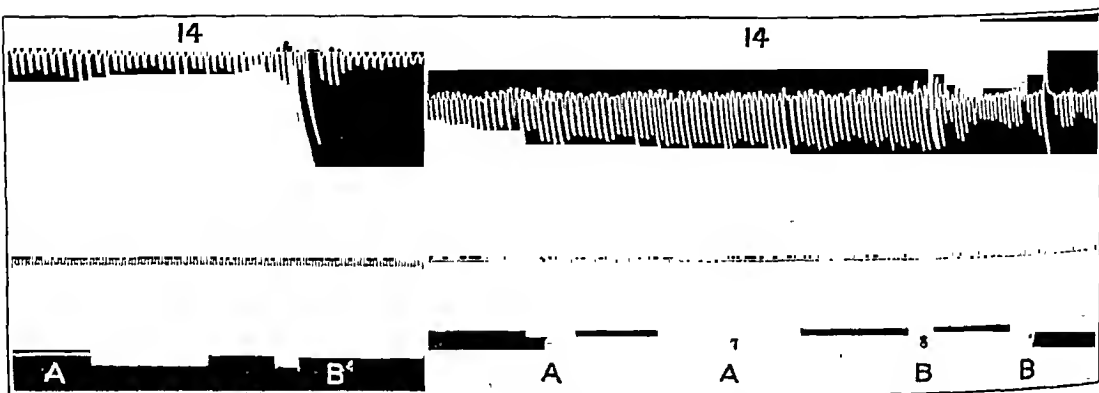
Fig. 7.—Respiratory tracings after removal of both stellate ganglions and the sympathetic trunks to the level of the fourth thoracic ganglions: *A*, coronary occlusion produced no evidence of any perception of the stimulus. *B* shows an immediate response to pinching of a toe pad.

ganglion was not wholly removed. In the cases of paravertebral injections of alcohol, in which these same fibers have been adequately blocked, there has also been complete relief of cardiac pain.

6. *Laminectomy and Section of Spinal Roots.*—In a series of five dogs the upper dorsal lamina were removed and a varying number of spinal roots were cut. Two or three days later the dogs, which appeared to have fully recovered from the effects of operation, were tested by temporary obstruction of the descending branch of the left coronary artery. Figure 8 shows that neither cutting the third to the seventh or

18. White, J. C.: Angina Pectoris: Treatment by Paravertebral Alcohol Injection or Operation Based on the Newer Concepts of Cardiac Innervation, Am. J. Surg. **9**:98, 1930.

the first to the fourth posterior roots on the left side nor cutting the upper four dorsal roots bilaterally prevented the sensation of pain. However, dog 18 (fig. 9) showed no signs of pain after the upper five anterior and posterior roots were cut bilaterally. In dog 19, in which the upper five posterior roots were cut bilaterally (with the exception of one small fiber of the third root on the right side), no symptoms of cardiac pain could be elicited.

These observations point out another possible method of relieving the pain of angina pectoris in man. There should be no need for cutting roots above the first thoracic, because, as pointed out, this is the highest segment that receives a white ramus communicans, and there are no higher connections between the cervical sympathetic trunk and the spinal cord. However, it is possible that in certain types of angina
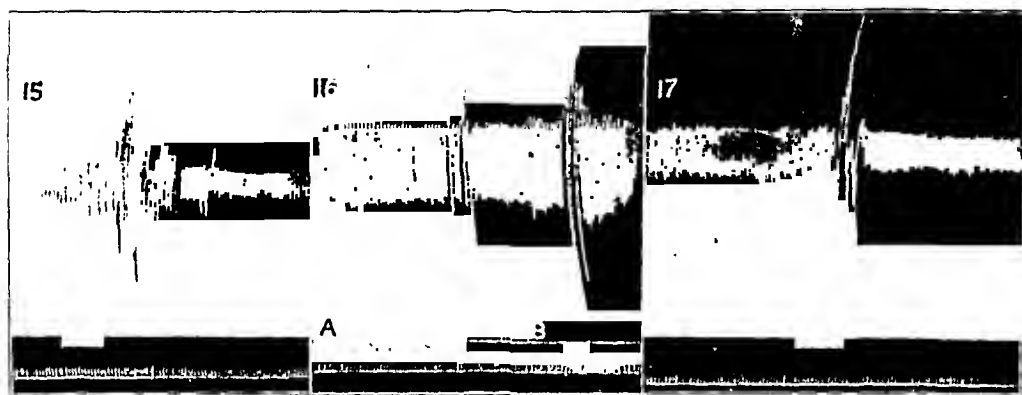
Fig. 8.—Results of cutting posterior spinal roots. Dog 15: Posterior roots, from third through seventh dorsal, cut on left. A marked response occurred to coronary occlusion. Dog 16: Posterior roots, from first through fourth dorsal, cut on left. A slight response occurred to coronary occlusion. (*A* indicates occlusion; *B*, pinching of a toe pad.) Dog 17: Posterior roots, from first through fourth dorsal, cut bilaterally. There was a definite response to coronary occlusion.

that are felt low down in the thorax or upper part of the abdomen, additional roots would have to be cut below the fifth thoracic segment.

7. Intercostal Neurectomy.—Weiss and Davis [19] have reported that in angina pectoris, as well as in other types of visceral pain, blocking of skin sensation entering the cord from any given area of referred pain may cause the pain to stop. One of the first methods of attacking angina pectoris surgically was by the section of intercostal nerves (Danielopolu [6]). This method was unsuccessful. In dog 20 (fig. 10) the upper five intercostal nerves on both sides were cut just distal to the point of origin of the sympathetic rami. This procedure was with-

19. Weiss, S., and Davis, D.: The Significance of the Afferent Impulses from the Skin in the Mechanism of Visceral Pain, Am. J. M. Sc. 176:517, 1928.
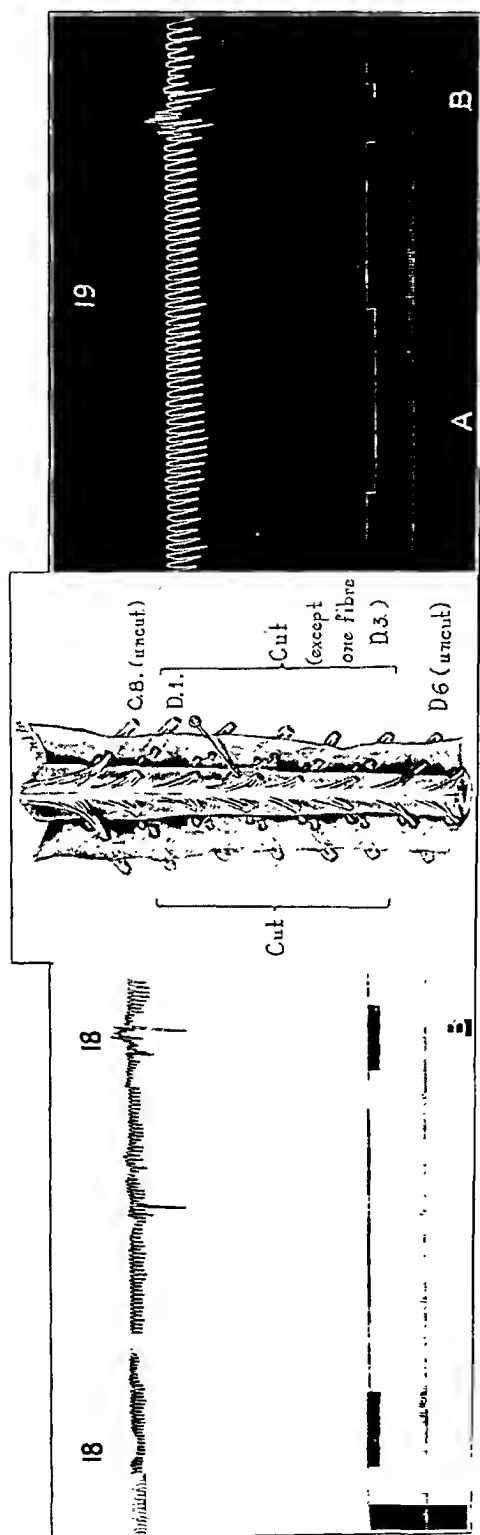
Fig. 9.—Respiratory tracings following operation. Dog 18: Anterior and posterior roots, from first through fifth dorsal, cut bilaterally. Dog. 19: Posterior roots, from first through fifth dorsal, cut bilaterally. The operation illustrated in sketch shows a single fiber from the third dorsal root, remaining uncut on right side. In none of these animals was there any pain sensation when the coronary artery was occluded (A). That normal skin sensation remained intact is shown by the response to light pinching of the hind toe pad (B).

out effect in preventing cardiac pain. Although this does not rule out the possibility that the dog might have felt visceral pain from afferent stimuli coming over the lower intercostal nerves, and that it might have been blocked if all these had been cut, this method could not be utilized for interrupting angina pectoris in man because it would be undesirable to cut such a large number of intercostal nerves.

8. *Bilateral Section of Vagus Nerves.*—It is a well known fact that the vagus nerve carries certain afferent impulses from the viscera to the central nervous system. In certain cases in which it has a well

TABLE 2.—*Efficiency of Various Neurosurgical Procedures in Interruption of Cardiac Pain Pathways in the Dog*

	Dog	Operation	Reaction to Occlusion of Coronary Artery
Controls	1	....	+++
	2	....	+++
	3	....	+++
	4	....	+++
Unilateral sympathectomy	5	Stellate (L)	+++
	6	Stellate through D4 (L)................................	+
	7	Stellate through D5 (L)................................	+++
Bilateral sympathectomy	8	Bilateral stellate	++
	9	Bilateral stellate	++
	10	Bilateral stellate	++
	11	Bilateral stellate	+
	12	Bilateral stellate	++
	13	Bilateral stellate	++
	14	Bilateral stellate, through D4.........................	0
	15	Posterior root section, D3-D7 (L)......................	+++
	16	Posterior root section, D1-D4 (L)......................	+
	17	Posterior root section, D1-D4 (R and L)................	+++
	18	Anterior and posterior root section, D1-D5 (R. and L.)	0
	19	Posterior root section, D1-D5	0
	20	Intercostal nerves, D1-D5 (R and L)....................	+++
	21	Division of vagi (R and L).............................	+++

defined depressor branch to the heart, Hofer[7] has reported good results from sectioning this depressor nerve. Other surgeons, however, have injected procaine hydrochloride directly into the vagi during attacks of angina pectoris, without relief. That bilateral section of the vagi has no effect on cardiac pain is clearly shown in figure 10 (dog 21).

In table 2 the effects on transmission of cardiac pain brought about by these various neurosurgical procedures are summarized. It is apparent that section of both vagi or of the upper intercostal nerves and resection of both stellate ganglions are inadequate procedures to control angina pectoris. Only removal of the stellates and upper four thoracic ganglions or section of the upper five spinal roots is capable of blocking cardiac pain completely.

EXPERIMENTAL METHODS FOR DETERMINING CARDIAC MOTOR PATHWAYS

Before the presence of direct connections between the upper thoracic ganglions below the stellate with the posterior cardiac plexus had been demonstrated anatomically by Jonnesco and Enarchesco,[15] Braeucker [16] and Kuntz and Morehouse,[17] Cannon, Lewis and Britton [20] had shown the presence of motor fibers running between these structures by physiologic methods. In their attempt to produce a completely denervated heart they continued to find marked degrees of cardiac acceleration after removal of both stellate ganglions, section of both vagi, denervation of the liver and removal of the adrenal medullas. It was only after the
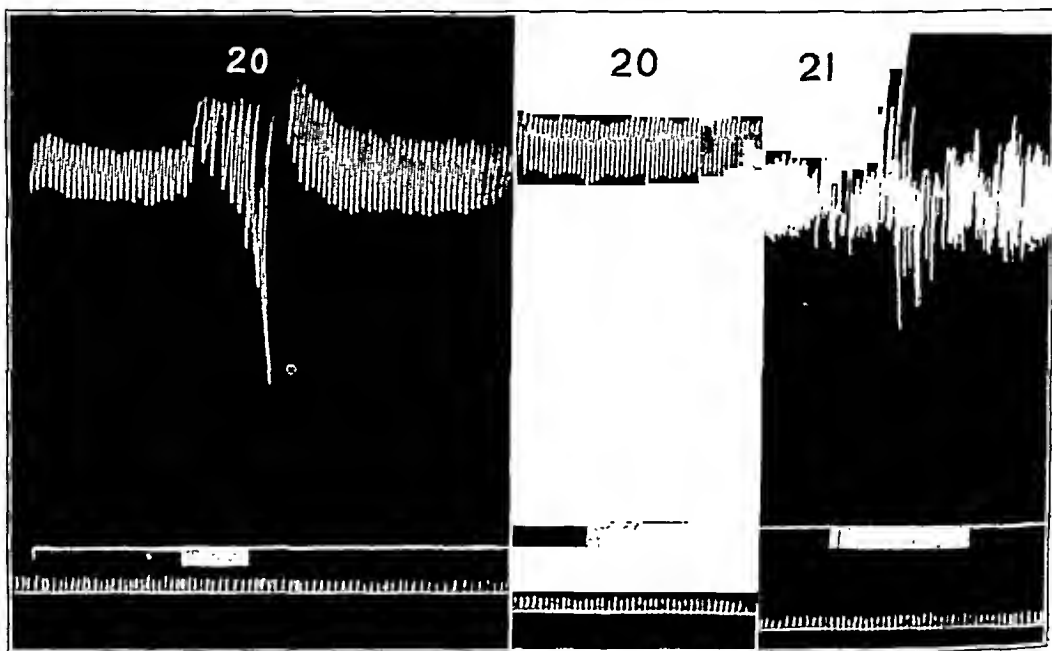
Fig. 10.—Respiratory tracings following operations. Dog 20: Bilateral section of upper five intercostal nerves just distal to the point of origin of the sympathetic rami. *A*, a marked response occurred to coronary occlusion. *B*, pinching of the skin over the upper thoracic wall proved anesthesia to have been complete. Dog 21: Bilateral section of vagi. Characteristic response on occlusion of coronary artery for twenty-five seconds.

upper thoracic ganglions had been removed on both sides that the heart failed to accelerate with emotional stimuli.

We have been able to show the presence of such connections by direct faradic stimulation of the ganglions. In a series of eight dogs

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20. Cannon, W. B.; Lewis, J. T., and Britton, B. W.: A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion with Evidence for Accessory Accelerator Fibres from the Thoracic Sympathetic Chain, Am. J. Physiol. **77**:326, 1927.

the upper sympathetic ganglions were exposed through the axillary incision already described. Pentobarbital sodium anesthesia was used in each case. Intratracheal insufflation of air prevented collapse of the lung in those cases in which the pleura was inadvertently opened. In the anesthetized animal the ganglions were stimulated intact and also after cutting the sympathetic trunk below the stellate ganglion. Stimulation was made both of the stellate ganglion above and the second and lower thoracic ganglions below. The stimulation was made with a tetanizing current produced by an induction coil, in which the secondary coil was set at distances varying between 7 and 10 cm. from the primary coil. With this arrangement there was no spread of current to the

TABLE 3.—*Results of Direct Faradic Stimulation of the Ganglions* *

Dog		Stellate		Second and Third Thoracic	
		Right	Left	Right	Left
22	Heart rate.....	Not done	201-228 11%	Not done	
	Blood pressure	Not done	79-145 80%		
23	Heart rate.....	126-222 78%	162-228 40%	Not done	
	Blood pressure	83-111 33%	127-144 14%		
24	Heart rate.....	132-240 80%	138-216 58%	Not done	
	Blood pressure	98-144 47%	105-151 44%		
		(a) Cord Cut at C3	(b) Vagi Paralyzed	(c) Adrenals Cut Out	
25	Heart rate.....	147-258 75%	156-276 77%	156-300 92%	
	Blood pressure	123-193 57%	114-131 15%	93-107 15%	
26	Heart rate.....	105-198 88%	120-156 30%	111-114 3%	186-198 7%
	Blood pressure	161-187 16%	167-177 6%	160-150 —6%	176-164 —8%
27	Heart rate.....	144-168 17%	150-180 20%	156-180 16%	108-168 55%
	Blood pressure	154-206 32%	148-184 26%	165-205 24%	136-180 32%
28	Heart rate.....	87- 96 10%	126-132 5%	84-108 28%	99- 99 0%
	Blood pressure	126-135 7%	163-165 1%	141-128 —8%	158-160 1%
29	Heart rate.....	168-168 0%	174-180 4%	168-264 58%	168-234 39%
	Blood pressure	173-175 1%	166-164 —1%	163-175 7%	174-194 11%

* These figures represent the maximum responses obtained from faradic stimulation of the stellate ganglions and sympathetic trunk below. The trunk was cut between the first and second thoracic ganglions.

adjacent muscles. Stimulation was performed both with the vagi intact and also after both vagi had been sectioned in the neck or paralyzed with atropine. The blood pressure and heart rate curves were graphically recorded and the percentage increase in heart rate after stimulation computed as an index of cardiac acceleration. These findings are summarized in table 3.

Examination of these protocols shows that in animals stimulation of the stellate ganglion produced marked cardiac acceleration and often a considerable increase in blood pressure. It might be claimed that this pressor effect could have been brought about by afferent somatic stimuli ascending to the cerebral centers and causing a reflex vasoconstrictor response or by stimulation of the adrenals with an outpouring of epinephrine. To rule out these possible complicating factors, the
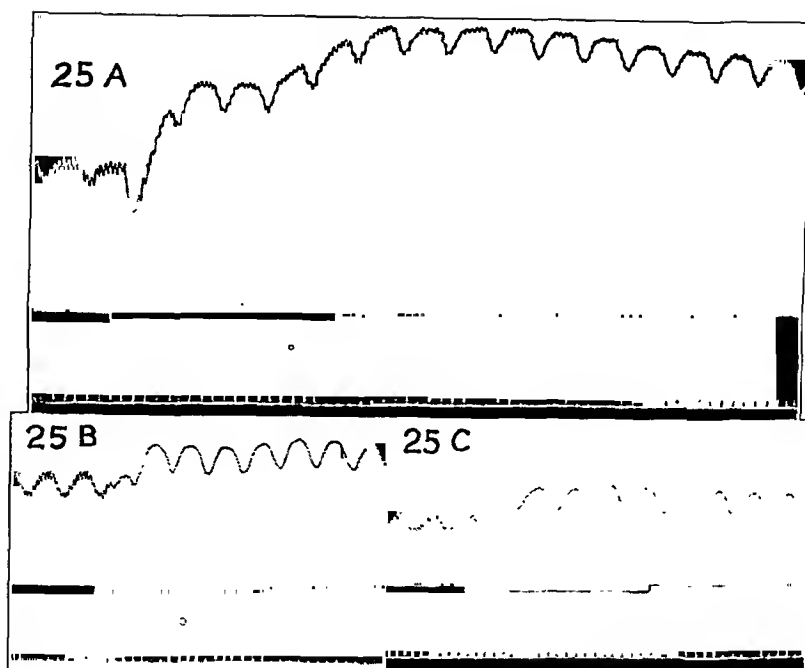
Fig. 11.—Cardiopressor response resulting from faradic stimulation of right stellate ganglion in dog 25. *A,* on stimulation after division of the spinal cord at third cervical segment, increase in heart rate, 75 per cent; in blood pressure, 57 per cent. *B,* on stimulation after paralysis of both vagi, increase in heart rate, 77 per cent; in blood pressure, 15 per cent. *C,* on stimulation after resection of adrenal glands, increase in heart rate, 92 per cent; in blood pressure, 15 per cent.
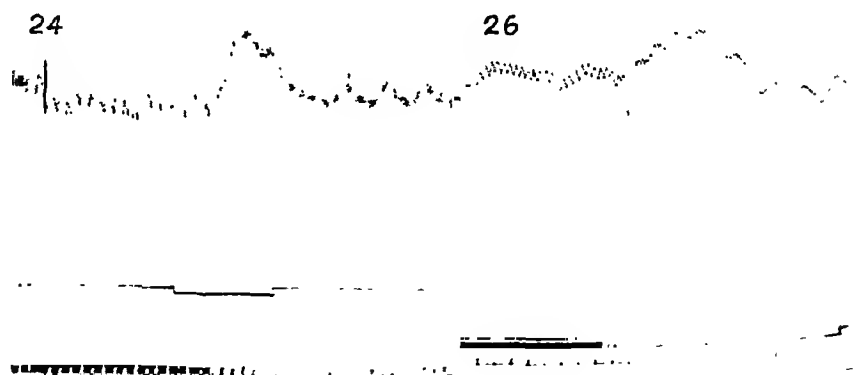
Fig. 12.—Cardiopressor response following faradic stimulation of the right stellate ganglion after division o the sympathetic trunk at its lower pole and paralysis of the vagi with atropine (in this and the following figure the time signal at the bottom of the graph marks the base line for the blood pressure; the middle line marks th duration of the stimulus: in dog 23, increase in heart rate, 78 per cent; in blood pressure, 33 per cent. Ir dog 24, increase in heart rate. 80 per cent; in blood pressure, 47 per cent. In dog 26, increase in heart rate 88 per cent; in blood pressure. 16 per cent.

spinal cord was cut at the level of the third cervical segment in dog 25, and later both vagi were cut and both adrenal glands removed. It was possible to keep this dog in fairly good condition by maintaining pulmonary ventilation through an inspiratory and expiratory pump. With the dog's head lowered, the systolic blood pressure did not fall below 100 mm. of mercury. With all possibilities of sensory reflexes eliminated, the vagi paralyzed and the adrenals removed, this dog still showed a tremendous (92 per cent) acceleration of the heart when the sympathetic ganglions were stimulated (fig. 11). In most of these
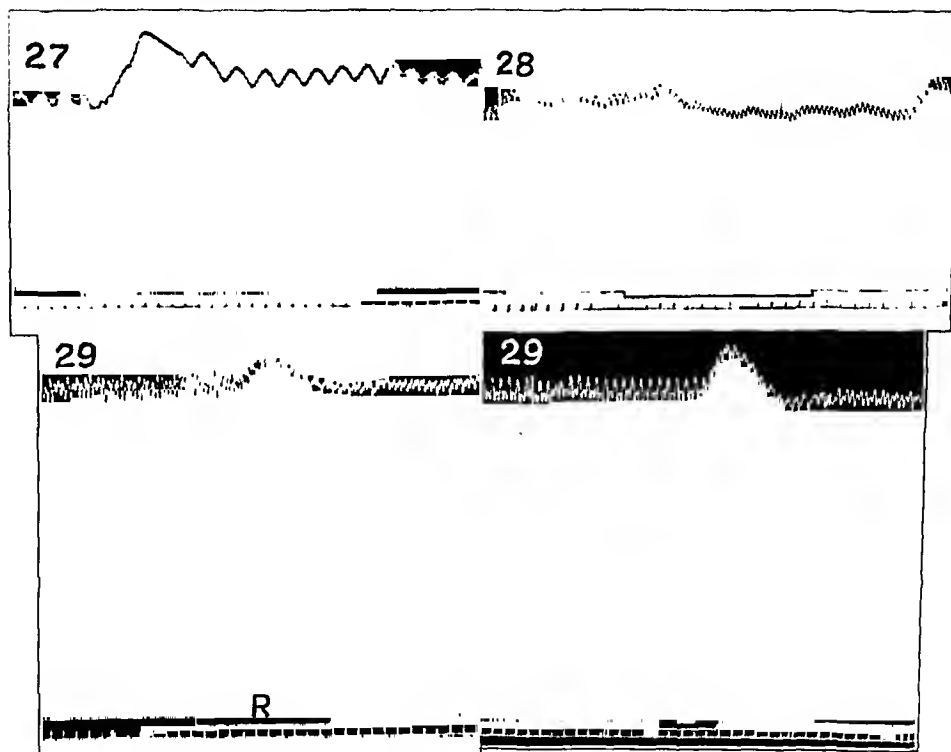
Fig. 13.—Cardiopressor response resulting from faradic stimulation of the second and third thoracic ganglions after removal of both stellate ganglions and paralysis of the vagus nerves with atropine. In dog 27, increase in heart rate, 55 per cent (left) ; in blood pressure, 32 per cent (left). In dog 28, increase in heart rate, 28 per cent (right) ; in blood pressure, —8 per cent (right). In dog 29, increase in heart rate, 58 per cent (right) and 39 per cent (left) ; in blood pressure, 7 per cent (right) and 11 per cent (left).

animals cardiac acceleration was greatest when the nerves on the right side were stimulated. No further increase resulted from bilateral excitation. The maximal acceleration of the heart rate on stellate stimulation was 92 per cent in dog 25 and from 88 to 78 per cent in dogs 23, 24 and 26 (fig. 12).

The maximal increase in cardiac rate when the lower thoracic ganglions were stimulated was 58 per cent. There was an acceleration of over 25 per cent on stimulating the lower ganglions in three of four dogs (fig. 13). It is furthermore interesting to note that in the cases of the greatest acceleration after stimulation of the lower ganglions there was a decided reduction of this response on stimulation of the stellate ganglions (dogs 27, 28 and 29). This phenomenon may well mean that while in a majority of cases the great preponderance of cardiac fibers run up through the stellate and the higher cervical sympathetic ganglions to reach the heart via the superior, middle and inferior cardiac nerves, in a smaller proportion of cases the lower transthoracic connections are of increased importance. In the first group cervical sympathectomy might well relieve the symptoms of angina pectoris, whereas in the second group relief would be slight or negligible. In summing up the results of these experiments on the cardiac accelerator pathways, it is again obvious that only an incomplete interruption of the pressor reflex can be achieved by limiting the operation to the removal of the cervical sympathetic down through the stellate ganglions. To interrupt effectively either the sensory or the motor pathways the operation must include the entire cervicodorsal ganglion and be continued down to the third or fourth thoracic segments.

COMMENT

While these experiments have definitely shown that in dogs there are important sensory and motor pathways connecting the heart with the spinal cord below the stellate ganglions, it is not necessarily safe to assume that these findings can be applied to man. In the clinical cases cited here, however, we have had a number of striking experiences which lead us to believe that the innervation of the heart in men and dogs is the same in all essential respects.

In approaching the problem of angina pectoris in man surgically, there are theoretically three possible methods of attack:

1. Vasomotor: Prevention of vasoconstrictor spasm of the coronary arteries.
2. Motor: Interruption of cardio-augmentor reflex.
3. Sensory: Interruption of pain pathways.

The physiologic studies of Anrep and Segall,[21] recently corroborated by Danielopolu,[22] rule out the first method. These writers have shown by a series of carefully worked out physiologic experiments that the vasoconstrictor fibers to the coronary arteries run in the vagus nerves,

21. Anrep, G. V., and Segall, H. N.: The Regulation of the Coronary Circulation, Heart 13:239, 1926.

22. Danielopolu, D.; Marcou, I., and Proca, G. G.: Sur l'innervation des coronaires, Compt. rend. Soc. de biol. 107:419, 1931.
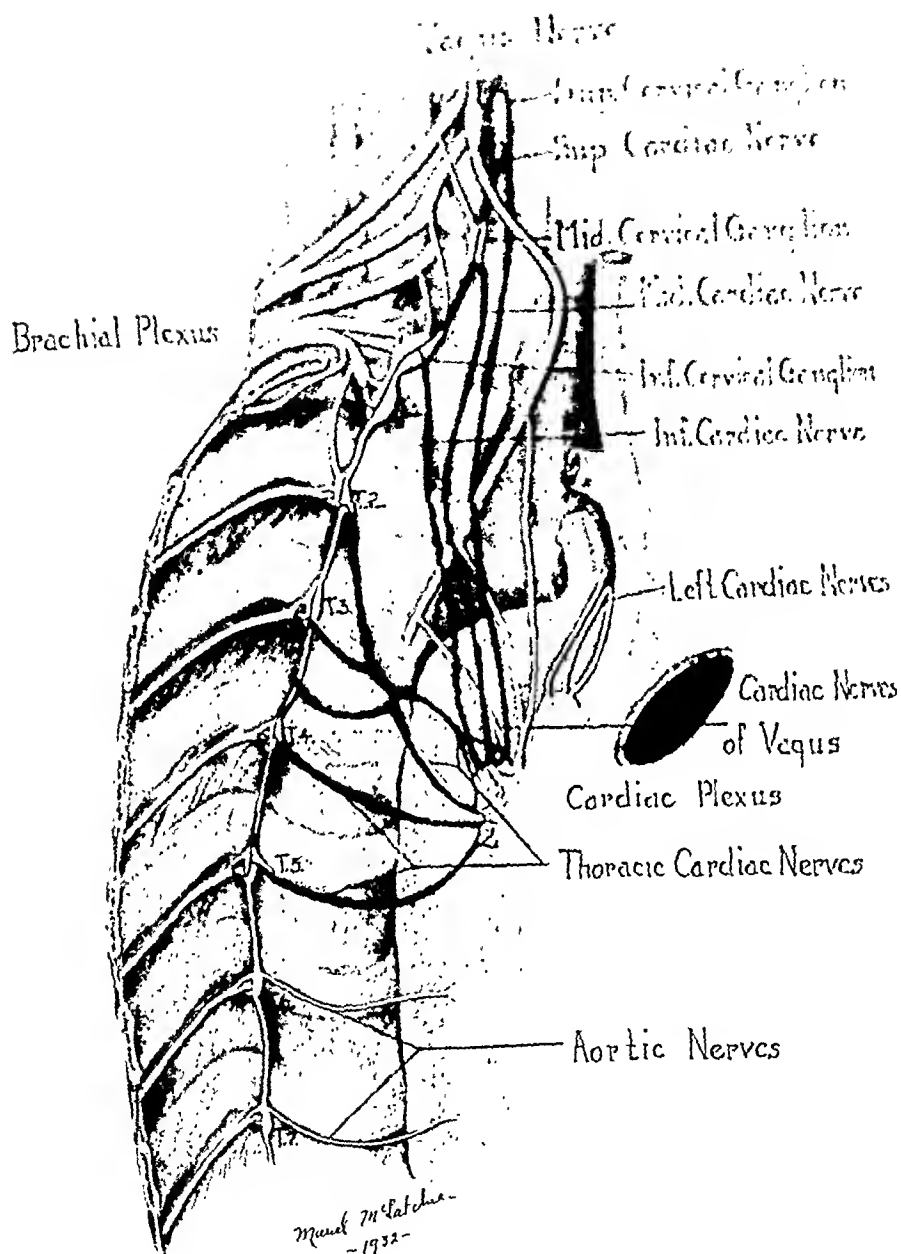
Fig. 14.—Diagrammatic presentation of the peripheral innervation of the heart. The sympathetic fibers are drawn in red. It is important to note that the only connections with the spinal cord are over the white sympathetic rami from the upper five thoracic ganglions (illustration modified from diagram in White, Paul D.: Heart Disease, New York, The Macmillan Company, 1931).

whereas the sympathetic system carries vasodilator fibers. As it is impossible to cut both vagi, interruption of the vasoconstrictor fibers is out of the question. A common explanation of the benefits produced by Coffey and Brown's operation of superior cervical ganglionectomy has been based erroneously on the theory that it prevents vasoconstrictor spasm of the coronary arteries. Just what the mechanism of this operation is remains somewhat uncertain, as Holmes and Ranson[23] have produced histologic evidence that the superior cervical ganglions transmit no afferent fibers. On the other hand, Heinbecker[24] has shown characteristic afferent electrical discharges on testing this ganglion with a cathode ray oscillograph. In our clinic superior cervical ganglionectomy has given inferior results, as only three of eight cases have shown improvement and the mortality has amounted to 12.5 per cent. As few favorable reports have been published in the recent literature, it would appear that this operation is being less frequently used.

Concerning the interruption of motor impulses to the heart which drive it to exceed its limited capacity for work, our experiments show that to accomplish this completely it would be necessary to remove all the sympathetic ganglions on both sides from the inferior cervical down through the fourth or fifth thoracic. A bilateral excision would be necessary, because we have shown that stimulation of the ganglions on either side gives nearly equal cardiopressor response. If this were carried out, the heart would undoubtedly be greatly crippled. Danielopolu, in his writings, has even advised against removal of the stellate ganglions, recommending only the cutting of their postganglionic rami to the brachial plexus and vertebral artery. This point of view is probably over-conservative, as we have excised the cervicothoracic and second dorsal ganglions many times in Raynaud's disease with no evidence of impaired cardiac efficiency. This is probably due to the fact that sufficient cardiac accelerator fibers run directly from the third, fourth and fifth thoracic ganglions to the heart to enable it to respond to its physiologic demands. Our clinical observations have even shown that in the presence of advanced degenerative cardiac disease and angina pectoris all the cardiac nerve connections can be safely blocked on one side, allowing the nerves on the opposite side to regulate the activity of the heart.

We have always maintained that the logical point for surgical attack is the sensory pathway. If our arguments in favor of this method are substantiated, the next point to be considered is the most feasible method of interrupting the nerves which transmit cardiac pain. Figure 14

23. Holmes, W. H., and Ranson, S. W.: Surgical Sympathectomy in Angina Pectoris, J. Lab. & Clin. Med. **10**:183, 1924.

24. Heinbecker, P.: Recent Advances in Our Knowledge of the Sympathetic Nervous System, J. Thoracic Surg. **1**:233, 1932.

shows in diagrammatic form the anatomic arrangement of these fibers. In some cases the majority of painful stimuli probably traverse the middle and inferior cardiac nerves and can be reached through the old type of cervical incision. In other cases, however, severe pain can still enter the central nervous system by the lower pathways, which are out of reach of the operator who makes his incision in the neck. The surgeon who uses the cervical approach is under an additional handicap because of the complexity of the sympathetic nerve structures in this region and their frequent anatomic variations. Examination of the diagram shows that all of the cardiac fibers converge in the upper thoracic ganglions and then enter the spinal cord over the white communicant rami and the posterior roots. They can be completely interrupted by blocking either the ganglions, the rami or the spinal roots. All of these pathways are definite structures and show few variations in their arrangement.

In the Massachusetts General Hospital during the past five years twenty-seven patients with angina pectoris have been treated along the lines just described. The patients have been selected purely on the basis of the intensity of their pain, and only those have been accepted who have not responded to medical treatment and who have continued to suffer so severely that they felt that the pain was unendurable. Neither the history of recent coronary occlusion nor active decompensation has been considered as a contraindication to the injection of alcohol. While surgical excision of the upper thoracic ganglions has given nearly perfect relief of pain on the side of operation,[25] this is probably too dangerous an operation to be used in patients with advanced coronary disease. Although there have been no early postoperative fatalities, two out of four patients have died within a month of operation, one of empyema following pneumonia and the other of coronary occlusion. The paravertebral injection of alcohol, on the other hand, is a reasonably safe surgical procedure. The results in these cases are summarized in table 4. Examination of this table shows that the method is capable of giving nearly complete relief in half the cases and of converting the severe forms of angina pectoris into milder types which can easily be controlled by medical measures in another 30 per cent. In the remaining 20 per cent of cases pain has not been satisfactorily relieved. In each of the latter complete anesthesia of the intercostal nerves has not been produced and it has been evident that failure has been due to the technical difficulty of performing a perfect injection. Our statistics here are in accord with those of other clinics and show that injection of alcohol

25. Our clinical experience has shown without exception that alcohol block or resection of the ganglions on a given side is capable of relieving cardiac pain on that side only. There is no justification for the belief that sympathectomy should be performed on the right side when it has failed to relieve the attacks on the left.

is undoubtedly the safest surgical method of treating angina pectoris and one which rests on a sound physiologic basis. Owing to the inherent difficulties in the technic, about one case in five is doomed to failure. It is also only fair to point out that following injection there is usually a transitory period of alcoholic neuritis of the infiltrated intercostal nerves. This may last from a few weeks to several months, and is particularly annoying in the cases in which a satisfactory result is not obtained.

In those cases of paravertebral injection of alcohol which fail, it would be difficult to carry out a dorsal ganglionectomy because the fibrosis produced by alcohol makes freeing of the pleura and exposure of the ganglions extremely difficult. Our experiments on animals show, however, that these cases can still be relieved by cutting the posterior spinal roots. This operation was recently performed by Loyal Davis [26] and was a complete success.

TABLE 4.—*Results of Twenty-Three Paravertebral Injections of Alcohol Performed in Massachusetts General Hospital* *

	Per Cent
Good (100 to 90% relieved)	47.8
Fair (90 to 50% relieved)	30.4
Improved (50 to 25% relieved)	8.7
Failures	13.1
Deaths	0
Complications: troublesome intercostal neuritis	13.0

* These cases have been followed from five years to six months.

We hope that this study of the sensory and motor pathways of the heart will be taken as a mere beginning toward a physiologic understanding of the surgical problem of angina pectoris. With the recent advances in the anatomy of the cardiac nerves and the development of a method of producing the condition experimentally in animals, a more rational surgical therapy should soon evolve. A start has now been made along these lines, but much further clinical experience will be required to substantiate these theories completely.

SUMMARY AND CONCLUSIONS

1. Through the use of Sutton and Lueth's method of temporarily occluding a branch of the left coronary artery in dogs, we have found that the resulting ischemia of the heart muscle can be counted on to produce characteristic changes in the behavior of the animal which closely resemble the manifestations of angina pectoris in man. We have employed this procedure in a series of twenty-one dogs to test the effectiveness of various neurosurgical operations for interrupting the pathways of cardiac pain.

26. Davis, L.: Personal communication to the authors.

The specimens, I believe, are to be regarded as a variation in the normal form of the femur; in other words, as anomalies; whether or not any morphologic significance is to be attributed to them, I do not know. The marked symmetry is an interesting feature.

In comparing the condition of the femora of E 386 with normal or average conditions, I shall refer to my previous observations on the

Fig. 1.—Bones of the right lower extremity of E 386.

femur which were based on 100 pairs of bones, from white men, dissecting room material, and shall use the mean values of the combined right and left sides, 200 bones in all (Ingalls,[2] 1924).

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2. Ingalls, N. W.: Studies on the Femur: I. General Characters of the Femur in the Male White, Am. J. Phys. Anthrop. **7:**207, 1924.

EXTERNAL FEATURES

Except for their outward form and proportions, the bones of E 386 show nothing out of the ordinary on external examination. They are clean, hard, normally smooth and much whiter than most of our specimens, but with no evidences of inflammatory processes or other pathologic changes in the tissue; only in the upper part of the tibiae is there a slight roughening on the lateral surface. Indeed, one of the most striking features in regard to these bones is that the conventional anthropologic measurements, if unaccompanied by illustrations, would
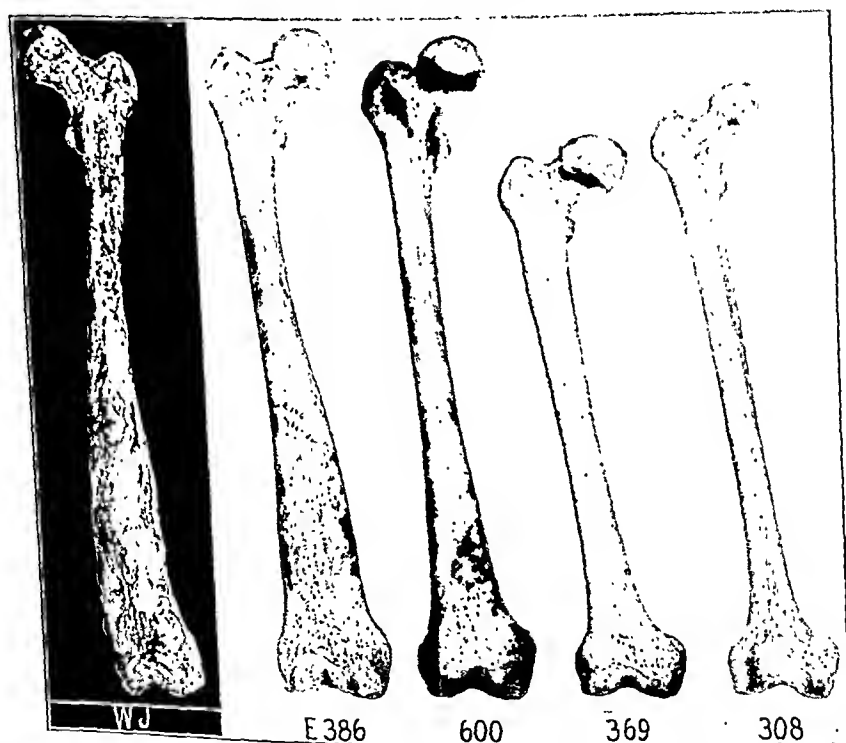
Fig. 2.—Series of femora to illustrate the varying configuration of the lower part of the shaft. *369* represents average conditions as far as the distal diaphysis is concerned. *308* shows a narrow lower end, which part, in *600*, is very broad. On the left (*W J*) is a reproduction of the Nubian femur, reported by Wood Jones, mentioned in the text; its length here is the same as that of *E 386*.

have given no indication whatever of the remarkable conditions obtaining in them. Except for the conspicuous enlargement in the lower part of the femur and the upper part of the tibia, there is nothing in these bones to attract attention.

The femora are quite long; the oblique length, measured in the natural position of the bone, is 514.5 mm. on the right and 516 mm. on the left, about 50 mm., or 2 inches (5 cm.) above the average, but definitely

below the maximum of our series of 100. The right tibia has a maximum length of 448 mm.; the left is a trifle shorter, 447 mm.; not only are the tibiae very long, but they are probably disproportionately long for the femur. Both the femur and the tibia, we believe, are definitely longer than they would have been if their normal growth had not been disturbed, but the overgrowth seems to have affected the tibia rather more than the femur. In both cases, moreover, the extra length seems to have been added in that part of the bones adjacent to the knee joint, rather than being more evenly distributed throughout. Since the bones of both the right and the left side present practically identical features I shall not make any special reference to either side.

As may be seen in the accompanying figures (figs. 1, 2 and 3), the lower femoral shaft, in somewhat more than half its extent, shows a marked increase in width; its internal border, just below the center of the bone, is also much more sharply convex than usual, and at the same time the anteroposterior dimensions are definitely increased. The unusual, and really abnormal, proportions of this part of the diaphysis are most clearly brought out if the transverse diameters are compared with certain other dimensions which are still perfectly normal. For this purpose the epicondylar, or bicondylar, width is especially useful, since it is measured transversely across the bone, just below the region in question, and also because it is the most constant, least variable measurement which can be taken on the femur. Omitting actual figures, it may be said that the transverse diameters of the lower diaphysis in this case are approximately 50 per cent above those seen in the average, normal specimen. For example, in the average bone the transverse diameter of the shaft, from 4 to 5 cm. above the margin of the articular surface in the midline, is about 41 mm.; in E 386, this measurement is 62 mm. The anteroposterior thickening is much less pronounced. If the posterior aspect of the bone is examined, it will be seen that the apex of the popliteal surface, indicated by the divergence of the lips of the linea aspera, is much higher in this bone than is usually the case. In the average femur the popliteal apex is a little over 120 mm. above the posterior border of the intercondylar notch. In our specimens it is in the neighborhood of 200 mm., for this is at best a rather uncertain measurement. It is this enormous increase in the popliteal length which, in conjunction with other characters, led us to suspect that the lower end of this bone is not only too wide but also much too long, as if the distal third had been stretched out to make the distal half. The abnormalities displayed by E 386 are sharply restricted to the lower diaphysis; the remainder of the bone, including the immediately adjacent knee joint, shows nothing which can be interpreted as abnormal or aberrant.

Much less will be said in regard to the tibia, since our acquaintance with this bone is rather less intimate and extensive than in the case of

the femur. Its proximal portion, almost if not quite half, is evenly and uniformly expanded, the increase in dimensions being rather more conspicuous in the transverse than in the sagittal diameter. In addition to this enlargement there is also a marked bowing of the bones, the most prominent part of the convexity being on the inner side just above the center. Except for being somewhat massive, in this respect matching the tibiae very well, the fibulae show no unusual characteristics.

In our series of 100 pairs of femora referred to, a few cases were encountered which showed a conspicuous widening of the lower shaft, e.g., specimen 600 (fig. 2), but nothing approaching either the absolute
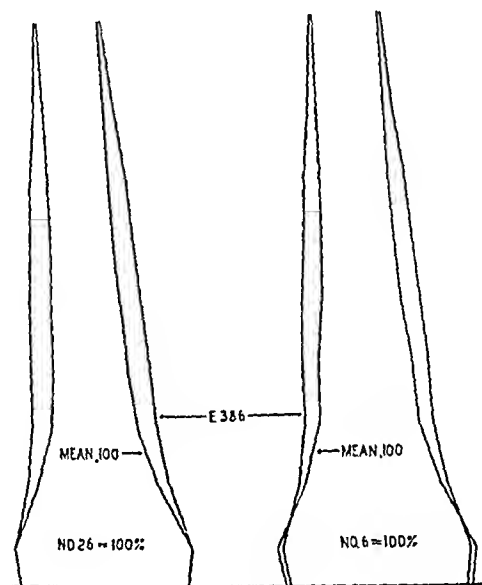
Fig. 3.—Schematic outlines of the lower half of the femur for E 386 and for the mean values of our series of 100. On the left the dimensions are in terms of the same epicondylar breadth, N. 26; on the right, in terms of the same diaphyseal length, No. 6. It will be seen that the deviation in E 386 are confined to the lower part of the shaft.

or the relative proportions exhibited by E 386. We do not believe that specimen 600 is quite normal and would place it with E 386, not necessarily because of any common pathologic condition, but because the disturbance, whatever it may be, has picked out the same part of the bone. The only case in the literature, so far as we know, which might be compared with ours was found by Wood Jones in ancient Nubian material (fig. 2). "In body 45 : 240, an adult man of the archaic period from the large cemetery at Dehmit, the left femur and tibia had under-gone a very remarkable change. The lower half of the femur and the

upper half of the tibia have become greatly enlarged and thickened."[3] In this case the surface of the bones was roughened and irregular, but the knee joint was not involved. Apparently the condition was unilateral in this case, something one would hardly expect, but of this we cannot be certain. The rarity of this condition is indicated by the fact
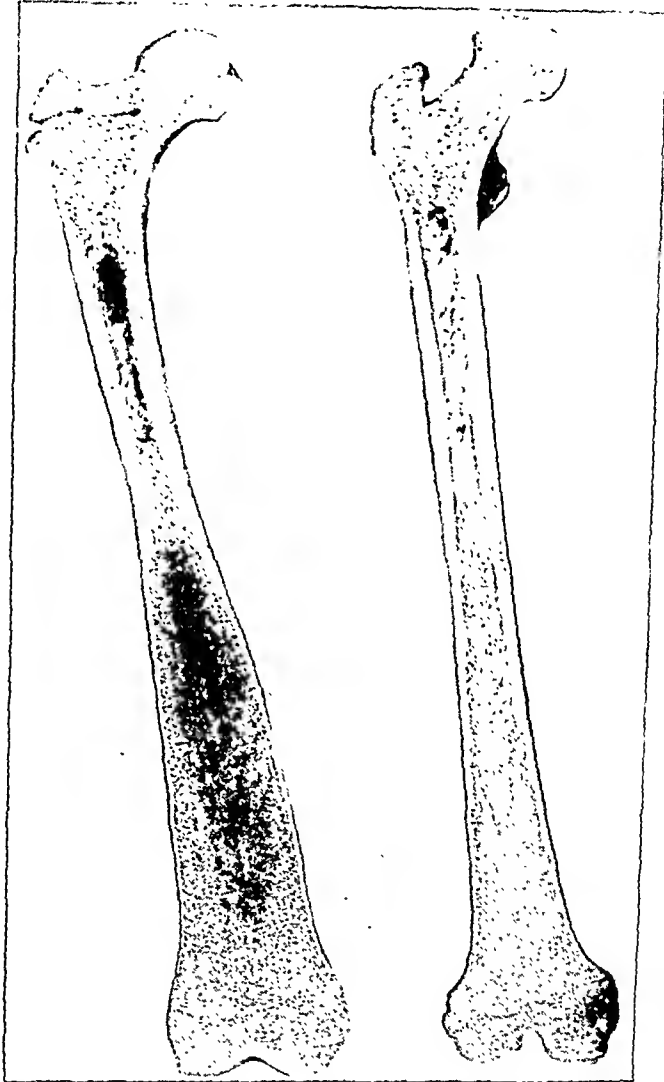
Fig. 4.—Frontal section of the left femur of *E 386* and a control section of the femur of approximately the same length, to show the excessive amount of cancellous bone and the short medullary cavity.

that it was unique among 6,000 bodies; for this reason also the suggested diagnosis of syphilis was considered to be rather hazardous.

3. Smith, G. E., and Jones, F. W.: The Archaeological Survey of Nubia: Report for 1907-1908; Report on the Human Remains, Cairo, 1910, vol. 2, p. 289, plate XLVIII, fig. 4.

INTERNAL ARCHITECTURE

Longitudinal sections through the left bones of E 386 show that the disturbance in this case has affected the entire thickness of the shaft, from the center to the periphery (fig. 4). The conditions found were quite unsuspected and were not known at the time of Dr. Hamann's original description. The most striking feature presented by these sections is the enormous amount of cancellous bone and the extremely small, short, medullary cavity. Ordinarily, the medullary cavity of the femur extends throughout most of the shaft, although its extent seems to be subject to considerable variation. Variable also are the amount, character and arrangement of the spongy bone which bounds the cavity and which may encroach on it to a considerable extent. From the specimens we have examined, it would appear that the upper limits of the marrow cavity are rather more definite and constant near or just below the lesser trochanter than they are at the lower end. In some cases the cavity extends below, almost to the old epiphyseal line, while in others it terminates at a much higher level. In E 386 the medullary cavity is only about 8 cm. long, not over a third of what might be found in much shorter bones; it is also situated high up, above the center of the shaft, and its limiting walls show unusual amounts of spongy bone. The dense bone of the shaft, at the level of the marrow cavity, is thicker than in most bones, while the cortical layer in the distal portion is thinner. This thinning of the cortex below is doubtless due to the great mass of internal cancellous tissue which makes a normally thick, supporting cortex unnecessary. Extending axially through the cancellous tissue which fills the lower half of the bone there is a broad zone, obviously a continuation of the marrow cavity, in which the spongy bone is somewhat less dense than elsewhere and is distinctly more irregular in structure.

Similar conditions obtain in the tibiae. The marrow cavity is little, if any, longer than in the femur; here, as contrasted with the femur, the cavity is below the middle of the bone, the proximal half being filled with cancellous tissue a little less dense than that in the bone above.

The only significant features in regard to this cancellous tissue are the increase in amount and density and the restriction of these changes to the portions of the bone immediately adjacent to the knee joint. While it can hardly be said that the osseous tissue involved is pathologic or abnormal in any way, there are certain secondary changes in the spongy bone which seem to be the direct result of the greater amount of bone present. These changes manifest themselves as a greater irregularity in the cancellous architecture. and one misses. to some extent, the characteristic disposition and arrangement of the finer osseous lamellae. particularly in the upper end of the tibia. The reasons for this

would seem to be quite simple, for in this case, with a marked excess of supporting osseous tissue, there is not the call for its economical distribution in relation to the predominating physical strains and stresses.

ETIOLOGIC FACTORS

While it is possible that the bones that have been considered may depart in some way from the normal in their finer histologic structure or chemical composition, the most obvious disturbance is in the amount and disposition of bony tissue. In both femora and tibiae there has been an alteration in form and length, there has been an excess production of building material, and all of these changes have come about at one end, instead of being more evenly distributed. The fact that the conditions are bilateral and perfectly symmetrical is of particular significance. What the etiologic influences may have been, we cannot say; most likely we are dealing with a deep-seated, chronic derangement, possibly metabolic or in part endocrine, which has disrupted entirely the normal growth and differentiation in the distal femur and proximal tibia.

Although we have no suggestions to offer as to the etiology of the conditions described, we believe that it is possible to present evidence as to why these particular parts of the bones have been picked out. What the remainder of this skeleton might have been like, we do not know.

In one of our recent articles on the femur,[4] we called attention to the fact that the lower portion of the femoral shaft, particularly in its transverse diameter, is the most variable part of the bone. The variability here is about twice as great as it is a few centimeters below, across the condylar region, and is distinctly higher than it is in the middle of the shaft. This unusual variability may be explained as one of the results of the comparatively recent remodeling and readjusting that have taken place in the neighborhood of the knee joint in association with the assumption of the erect posture. The extensive and characteristic alterations that have been instituted in the phylogenetic development of the human knee, changes which have involved the soft parts, muscles, ligaments, etc., no less than the skeletal elements, have left this whole region, both structurally and functionally, in a distinctly unstable and vulnerable condition, and this susceptibility and vulnerability are especially in evidence in the lower femoral shaft. There is also evidence that the proximal portion of the tibia shares somewhat in the same general condition and for the same reasons.

An important aspect of this relative vulnerability, which in turn is an expression of the newness and as yet unstabilized conditions around

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4. Ingalls, N. W., and Grossberg, M. H.: Studies on the Femur: VI. The Distal Part of the Diaphysis, Am. J. Phys. Anthrop. **16**:475, 1932.

the knee, is the comparative frequency with which this part of the femur deviates more or less from normal and average conditions. Often enough these deviations take on a frankly pathologic character, and pathologic changes in the femur are usually found in the lower part of the shaft, in the tibia near its upper end. Specimen E 386, we believe, represents one of those cases, and they are by no means rare, in which definitely pathologic processes manifest themselves, frequently or by preference, in those organs or structures the phylogenetic past of which has left them relatively variable, unstable and vulnerable. A comparable state of affairs exists in the lumbar spine, also a region recently modified to suit the upright position, and here, again, defects and divers infirmities are especially frequent (Willis,[5]).

Additional data on E 386, more from the anthropologic point of view, and further comments on the general subject of femoral variability will be found in the article previously mentioned.[4]

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5. Willis, T. A.: Backache from Vertebral Anomaly, Surg., Gynec. & Obst. **43**:658 (May) 1924.

USE OF RIB GRAFTS FOR FUSION OF THE SPINAL COLUMN

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From the beginning of reconstructive and plastic bone surgery ribs have been transplanted not infrequently to promote union between bone fragments, to bring about fusion of adjacent bones and to bridge defects resulting from the loss of substance. Of their use in this latter rôle, Eloesser,[1] in 1920, contributed his experience with twenty-two cases involving bones of the extremities. He concluded that rib grafting was a feasible procedure, that ribs are more likely to survive in the presence of infection than the more dense massive grafts, that they are rapidly absorbed, and that they are particularly useful when no great demands are made on the strength of the graft (until replaced by new bone). He also observed that when used to repair large defects or when put under strain they were more prone to refracture than (full thickness) tibial grafts.

The first reference to the use of rib grafts for fusion of the spine was reported by Gutierrez[2] in 1924. In his six cases of vertebral tuberculosis, solid bony fusion was obtained, with subsequent arrest of the disease. Similar experiences were reported by Grantham[3] in 1927 and by Casacescu[4] in 1929. In the same year Whitman[5] and Kleinberg[6] reported the transplantation of ribs for osteosynthesis of the spine in cases of scoliosis. The ribs were removed primarily to reduce the posterior bulge of the thoracic cage resulting from the rotation of the spine. In most instances, as in the references noted, the grafts were preserved and transplanted at a second operation. From an experience with fifteen cases, A. Whitman[5] reported that the rib grafts were "rapidly replaced by an unusually heavy deposit of bone."

1. Eloesser, Leo: Rib Grafting Operations for the Repair of Bone Defects and Their End-Results, Arch. Surg. **1**:428 (Nov.) 1920.

2. Gutierrez, A.: Rib Implant in Tuberculous Spondylitis, Arch. franco-belges de chir. **27**:768, 1924.

3. Grantham, S. A.: Method of Spinal Fixation in Tubercular Spondylitis in Children, J. Bone & Joint Surg. **9**:748, 1927.

4. Casacescu, H.: Spinal Bone Grafts with Multiple Fragments of Ribs in Pott's Disease, Rev. de chir., Bucuresti **21**:143, 1929.

5. Whitman, A.: Rib Grafting for Scoliosis, Am. J. Surg. **6**:801, 1929.

6. Kleinberg, S.: Spinal Fusion in Scoliosis, J. Bone & Joint Surg. **11**:66, 1929.

The most important considerations in the selection of bone for transplantation are the relative inherent osteogenic properties and tensile strength. The latter factor is of no great consequence in the type of operation to be described subsequently.

COMPARATIVE OSTEOGENESIS

In comparing the respective osteogenic potentialities of ribs (cancellous bone) with the dense cortical bone of tibial grafts reference will be made to experimental observations reported in the literature and to some which were personally conducted. All observers are agreed that spongy bone undergoes absorption and is replaced by new bone sooner after transplantation and more rapidly than dense cortical bone. Their opinions diverge only in respect to the explanation of the phenomena as based on the two principal theories of osteogenesis.

In regard to the transplanted bone in animals. Gallie and Robertson,[7] advocates of the cellular theory, made the following observations:

The changes observed (in cancellous grafts) resemble those already described (compact bone) except that they have occurred much earlier and much more extensively. The bone cells in the lacunae all die and disappear, as described before, but the circulation is fairly well reestablished in one week. Not only do the surface osteoblasts survive, but the osteoblasts in the open Haversian canals for a considerable distance inward from the surface continue to live and functionate so that at the end of three weeks absorption is taking place in all directions through the graft and new bone not only surrounds the graft on its external surfaces but extends throughout its whole length and thickness. The picture is in marked contrast to that of the compact graft of similar age. Not only is this increased rapidity of absorption and replacement due to the increased number of active cells present, but it is also due to the greater ease with which the new blood vessels and osteoblasts can advance from the periphery to the center.

They believe that a greater number of cells survive because spongy bone is more cellular and more permeable to the nutrient lymph in which it is bathed. For this reason they stated that:

Theoretically the best bone to use would be cancellous bone such as a rib. But unfortunately this activity is directed primarily in the direction of absorption so that rib must not be used if any great strain is to be placed on it (where the gap to be filled is large).

Leriche and Policard,[8] exponents of the noncellular theory, stated that "transplants of spongy bone take better than do those of compact bone. The passage ways for the rehabilitation are larger and more per-

7. Gallie, W. E., and Robertson, D. E.: The Repair of Bone, Brit. J. Surg. 7:211 (Oct.) 1919.

8. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone: Its Problems, translated by Sherwood Moore and J. Albert Key, St. Louis, C. V. Mosby Company, 1928, pp. 124 and 166.

meable. . . . " They also stated that "all transplanted bone fragments die, resorb, and it is uniquely in dying that bone gives rise to new bone." Although less calcium is transplanted with cancellous bone, it is more accessible for liberation by the osteoblasts, and in consequence a "calcific surcharge" to the "ossifiable medium" is rendered earlier and more rapidly. To these views, in general, Bancroft,[9] Greig,[10] Murray[11] and others subscribe.

In an endeavor to compare the relative osteogenic properties of rib with tibial transplants with specific reference to their use in spinal fusion operations, two types of investigation were carried out, clinical and experimental.

CLINICAL HISTOLOGIC STUDIES

Since adequate fixation of a scoliotic spine frequently requires fusion of twelve or more vertebrae, the operation at the University of Chicago Clinics has usually been performed in two stages with an interim of approximately two weeks. From six of such cases sections of grafts placed at the first operation from ten to fourteen days previously were removed in the course of the second stage for histologic study. In each instance the graft had the appearance of dead bone, but was firmly fixed in edematous fibrous tissue to the bed of bone chips in which it had been placed.

These specimens, two of costal and four of tibial transplants, were decalcified and sectioned. In all instances the surfaces of the grafts were partially or entirely covered by loose cellular tissue with numerous round, fusiform and polygonal cells with long protoplasmic processes and an occasional multinucleated cell occupying a small cavity on the surface of the bone. In the open haversian canals on the free end of all grafts and about cancellous spaces of the ribs there was evidence of osteoblastic proliferation and an ingrowth of newly formed connective tissue with a network of capillaries. With the exception of one tibial graft there were small areas of fine trabeculae of new bone on both surfaces and in one rib graft, in several cancellous spaces. Definitely more new bone was present in the rib specimens.

The bone itself had essentially the appearance of necrosis. The lacunae were either empty or contained cells that were markedly shrunken and stained poorly. Except for a narrow peripheral border of living and proliferating cells, the blood vessels and cellular tissue were coagulated and undergoing autolysis. There was very little, but definite, evidence of beginning bone absorption.

9. Bancroft, F. W.: Bone Repair Following Injury and Infection, Arch. Surg. **5**:646 (Nov.) 1922.

10. Greig, D. M.: Clinical Observations on the Surgical Pathology of Bone, Edinburgh, Oliver & Boyd, 1931.

11. Murray, C. R.: The Repair of Fractures, Minnesota Med. **13**:137, 1930.
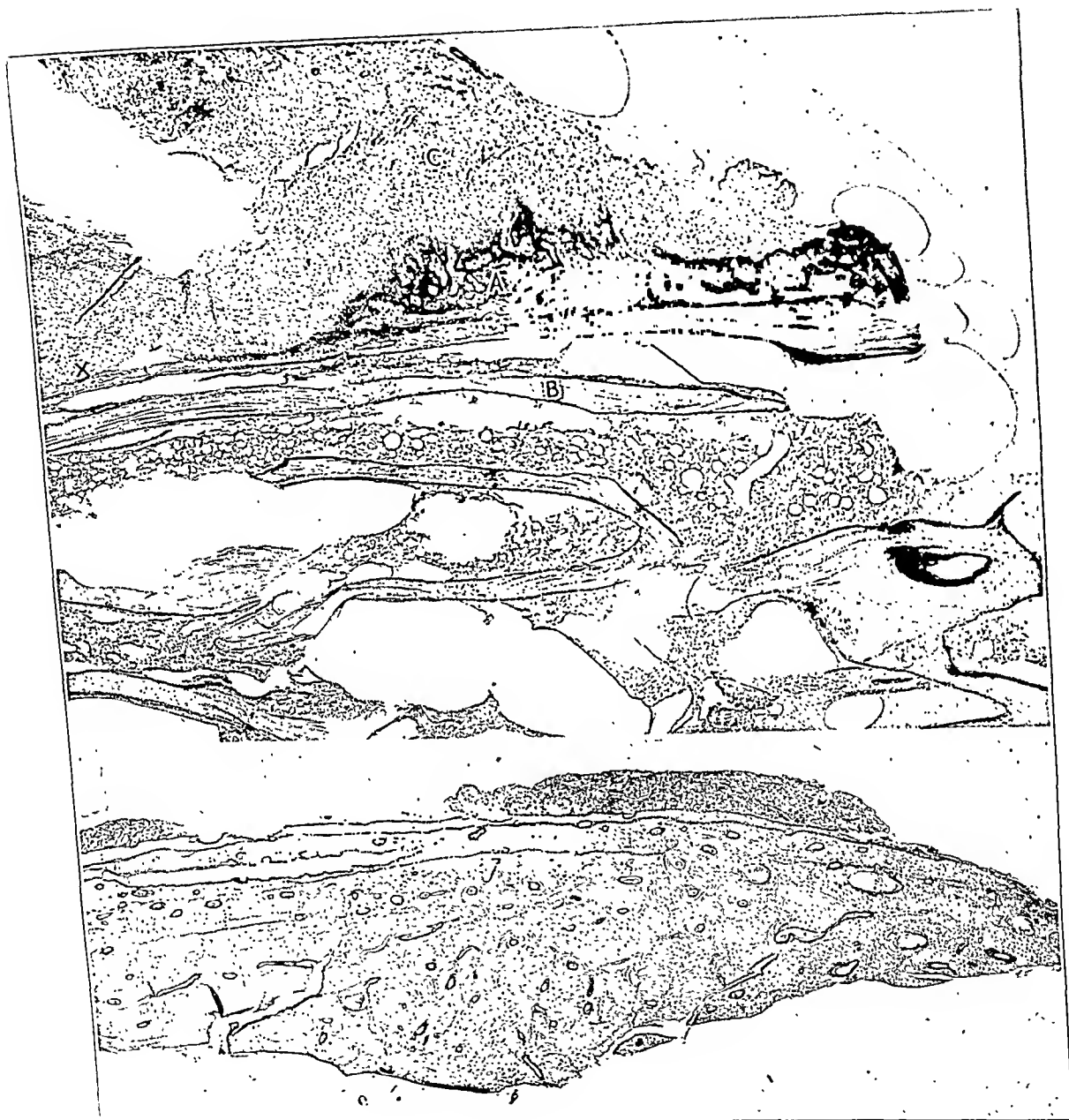
Fig. 1.—The upper photomicrograph shows a specimen from a thirteen day human rib graft in which superficial bone cells survived transplantation. *B'* represents the area in which these cells were found (see fig. 2). *A* shows the new bone overlying it; *C*, osteoid tissue; *B*, necrotic bone, and *X*, the area in which there were no living bone cells and no overlying new bone. Reduced from a magnification of × 25. The lower photomicrograph shows a section of a fourteen day human tibial graft. Living cells were found in the dense bone immediately adjacent to the deposits of new bone on the surface. In the intervening areas all lacunae were either empty or contained dead cells. Note the difference in structure of compact bone as compared to spongy bone (see upper photomicrograph). Reduced from a magnification of × 25.

In two of the specimens (one of each type of graft) a most interesting relationship was observed. As illustrated in figures 1, 2, 3 and 4 (rib graft), there were along the surface small areas of excessive deposits (compared to other specimens of the same age) of new bone separated by areas devoid of new bone. In the substance of the graft imme-

Fig. 2.—A higher magnification of the area marked B' in figure 1. The superficial living bone cells (E) stand out in sharp contrast to the dead cells in the deeper structure (B); the new bone (A) is deposited on the surface immediately over these cells. Reduced from a magnification of × 450.

diately underlying the trabeculi of new bone the lacunae contained living bone cells (figs. 2 and 3) which stood out in sharp contrast to the dead cells in the deeper structure and elsewhere along the surface (fig. 4), where there had been no new bone deposited. It is reasonable to assume

that this relationship of living transplanted bone cells to new bone formation is more than a coincidental occurrence. It speaks strongly for a function secretory or otherwise, inherent in osteoblasts and probably in other cells, which plays a constructive rôle in osteogenesis as opposed to the theory of a limited function of osteoclasis maintained by Leriche
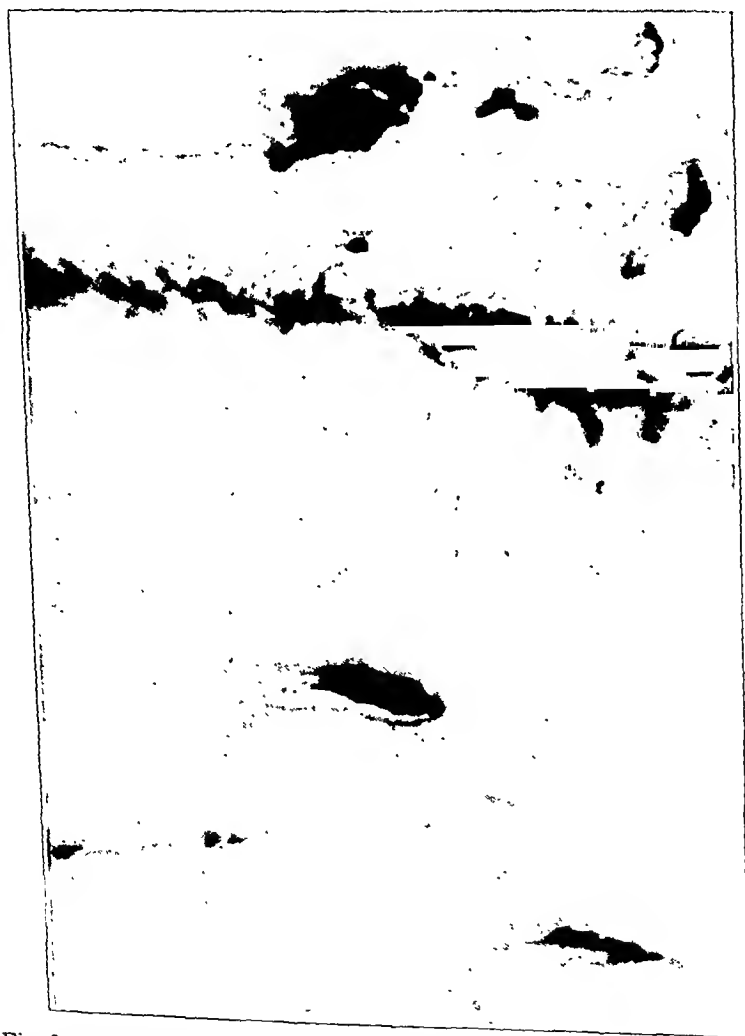
Fig. 3.—A higher magnification of the area labeled E in figure 2, to show living bone cells. Reduced from a magnification of × 2,600.

and Policard.[12] Despite encasement in bone, these cells presumably received sufficient nutrition to maintain cell life.

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12. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone: Its Problems, translated by Sherwood Moore and J. Albert Key, St. Louis, C. V. Mosby Company, 1928.

The slowness with which dense bone undergoes absorption and replacement by new bone is illustrated in figure 5. This section was removed from a full thickness graft from the cortex of the tibia which had been transplanted seven months previously to effect an Albee type
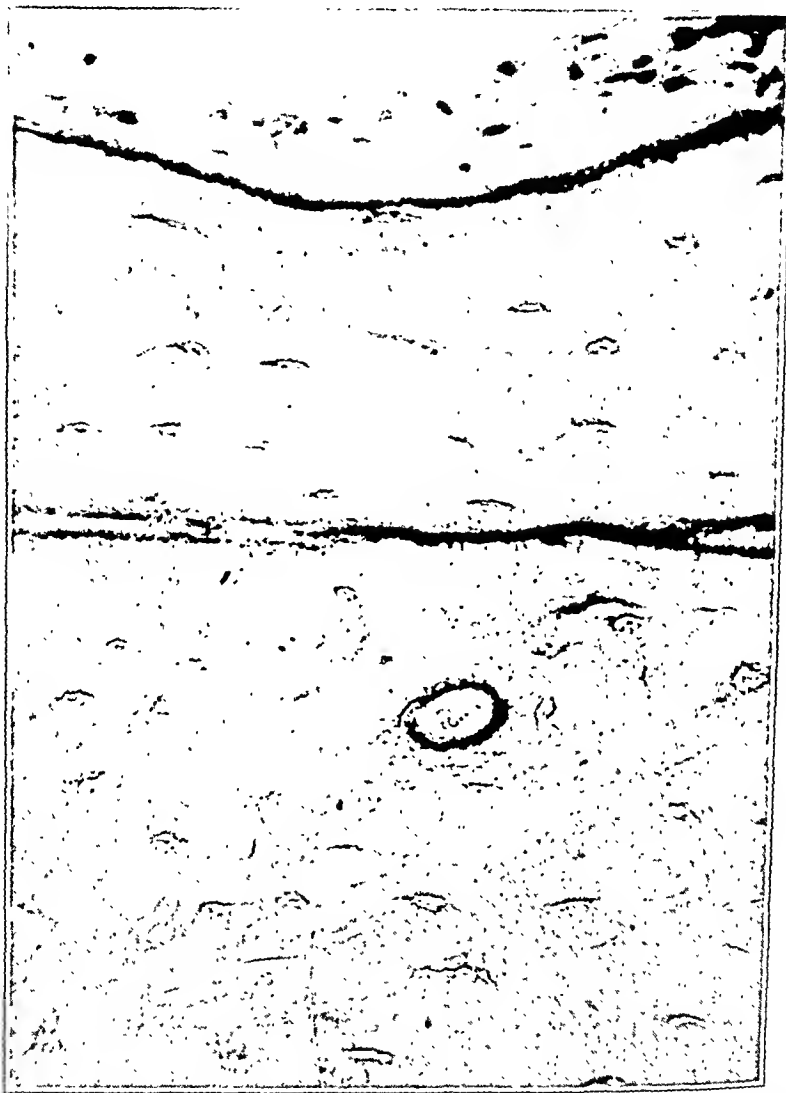
Fig. 4.—A higher magnification of the area labeled X in figure 1. All lacunae are either empty or contain dead cells. There was no new bone on the adjacent surface. Compare with figure 2. Reduced from a magnification of × 450.

of spinal fusion. Pseudo-arthrosis had developed in the graft near the middle of its span and necessitated a second fusion operation, at which time the specimen was obtained. It displayed all stages of the process

of creeping substitution (Barth [13] and Phemister [14]), extensive areas of dead bone, interspersed by areas of newly formed fibrous tissue and blood vessels and trabeculae of young new bone, while in other areas there was new bone undergoing reorganization and of an adult type. At the site of the pseudo-arthrosis there was no bone (old or new), and

Fig. 5.—Well organized new bone laid down in necrotic bone following invasion of granulation tissue, revascularization and absorption in the process of creeping substitution. Note unreplaced necrotic bone of a human tibial graft seven months after transplantation to the spine. Reduced from a magnification of $\times$ 450.

13. Barth, A.: Histologische Untersuchungen über Knochenimplantationen, Beitr. z. path. Anat. u. z. allg. Path. **17**:65, 1895.

14. Phemister, D. B.: Necrotic Bone and the Subsequent Changes Which It Undergoes, J. A. M. A. **64**:211 (Jan. 16) 1915.

the space was filled with dense fibrous tissue. It appeared that replacement with new bone had failed to keep pace with the process of resorption.

EXPERIMENTAL FUSIONS

In thirteen half-grown kids, sections of ribs and tibiae were transplanted to beds of bone chips turned out from the laminae and against the denuded surfaces of the laminae. In all but four animals the spinous processes were removed and discarded. The grafts were of sufficient length to bridge three vertebrae and consisted of transplanted segments of ribs in six animals, full thickness tibial transplants with periosteum
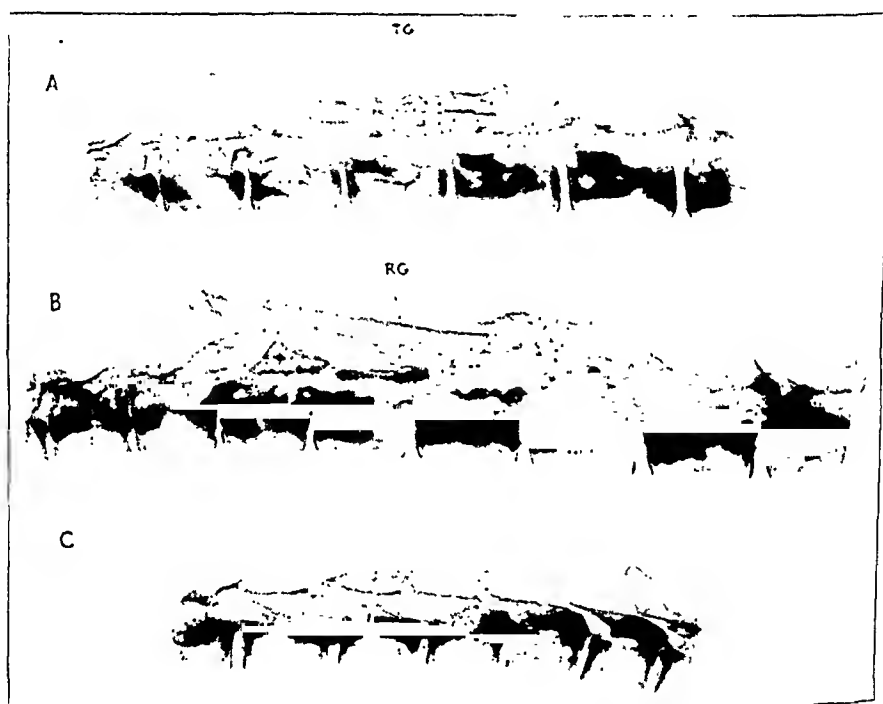
Fig. 6.—Roentgenograms of three spines ninety days after operation. *A*, a full thickness tibial graft. Note *TG*, unabsorbed necrotic bone of the transplant. *B*, infected rib grafts (*RG*), lying free in the abscess cavities; there was no invasion by granulation tissue; consequently there was a failure of absorption. The disastrous effect of a severe infection is well illustrated. *C*, a rib transplant entirely absorbed and replaced by new bone. Note the solid bony fusion.

in four animals and both rib and tibial grafts in three instances. No attempt was made to restrict the activities of the animals or to immobilize their spines after operation. They were killed at periods varying from seven days to five months, and microscopic sections from the areas in which the transplants had been placed were studied. In only one animal (fig. 6 *B*) was there a deep wound infection. In this instance the grafts acted as sequestrums floating free in the abscess cavities.

A chronological summary of the observations made in this group of experiments is as follows:

1. Three goats were killed seven days after operation. In one animal both tibial and rib grafts had been transplanted. The bone of all four transplants presented the usual appearance of necrosis. There was, however, considerable proliferation of the subperiosteal osteoblasts and of the cells on the endosteal surfaces of both tibial grafts and of one rib graft, which had been split longitudinally. On these surfaces there were also numerous capillaries with, in the split rib specimen, some invasion of the cancellous spaces.

In contradistinction to the tibial grafts, both rib transplants showed along the surfaces small areas of resorption with a few fine trabeculi of new bone.

2. Four similar specimens recovered from three animals at the end of two weeks revealed increased cellular proliferation with an ingrowth of capillaries in the formation of granulation tissue on all surfaces of the grafts. The tibial transplants presented the picture of beginning bone resorption and new bone formation as previously described and as observed in the rib grafts seven days earlier. The rib specimens displayed a more active and advanced stage of the same process. They were invaded rather extensively by granulation tissue, and definite deposits of new bone were in evidence.

3. Sections of each type of graft removed with the spines of two animals four weeks after transplantation revealed extensive absorption of the rib graft (fig. 7) with no increase in new bone as compared with that presented in the fourteen day specimens. The tibial transplant, however, had undergone much less absorption, but displayed about an equal amount of new bone. It appeared that at this stage in the rib specimen the process of absorption had greatly surpassed new bone replacement, whereas in the case of the tibial graft the two processes were more nearly keeping pace with each other.

4. In the comparative study of two sixty day specimens only small remnants of the dead rib could be discerned, and these were surrounded by an irregular mass of new bone which was continuous with that arising from the laminae. In contrast, the major portion of the tibial transplant remained unabsorbed, but likewise was surrounded by new bone which had established union with the laminae. The new bone laid down in and about the rib appeared to be greater in amount and somewhat more organized than that arising from the tibial transplant. This microscopic evidence of bony union and fusion was also demonstrable roentgenologically and by direct inspection.

5. Two animals were killed ninety days after operation. No vestige of the rib (fig. 6 C) could be found in the sections studied, but in its

place was a large mass of new bone, much of which was organized into an adult type. It appeared that the major portion of the tibial graft had been absorbed and replaced by new bone, but considerable dead bone (fig. 6 A) still remained in large irregular islands surrounded by

Fig. 7.—Rib graft thirty days after transplantation. The bone substance of the graft (B) is necrotic and undergoing rather extensive absorption and invasion by granulation tissue (D). There are numerous small deposits of new bone (A) and large areas of osteoid tissue with marked osteoblastic proliferation (C). The area (AA) represents new bone arising from the denuded surfaces of the laminae; × 30.

granulations and new bone. Bony fusion was apparent, as evidenced by continuity with new bone arising from the laminae.

6. One animal was killed one hundred and fifty-five days after operation and yielded two specimens for comparison. There were solid bony

fusion, no trace of dead bone of either the tibial or the rib graft and heavy deposits of new bone which were well organized and more dense than adult spongy bone.

In this series of experiments the bone, both dense and spongy, had without exception undergone necrosis. The cellular tissue on the surfaces and in open haversian canals and cancellous spaces of the trans-
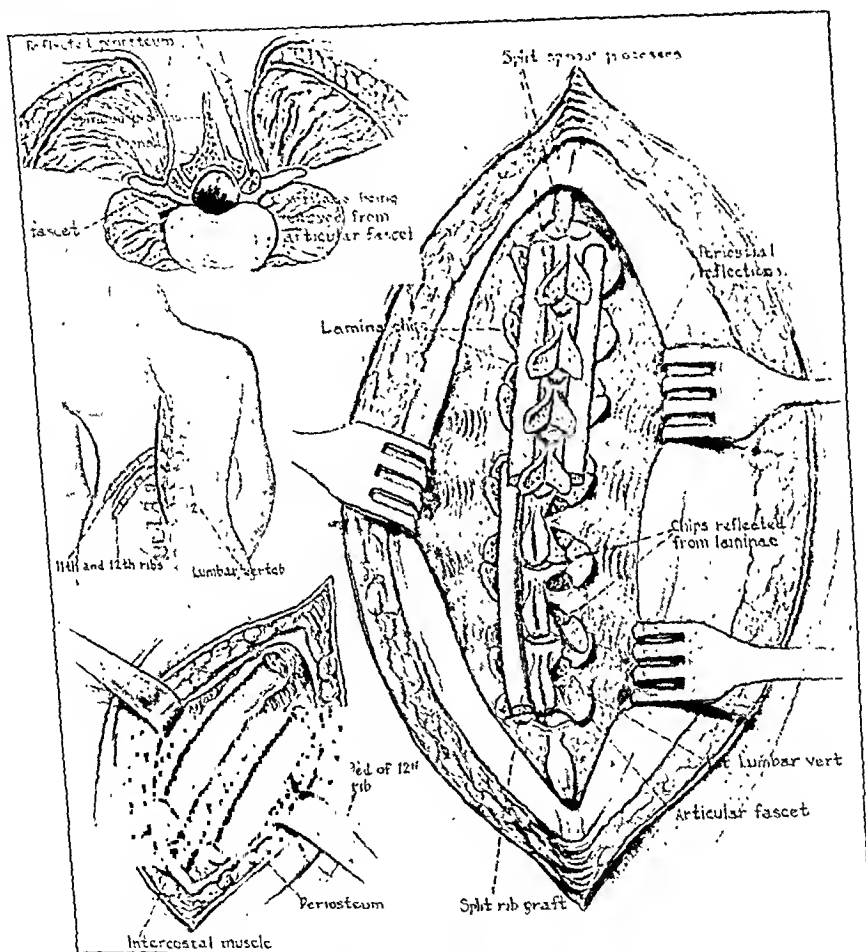
Fig. 8.—A modified Hibbs type of operation supplemented with rib grafts. The resected rib segments are split longitudinally and placed in the bed of overlapping fragments turned down from the laminae. The spinous processes are split and turned out over the transplants.

plants survived and within seven days showed considerable proliferation. The cells within lacunae, encased in bone, died and gradually disintegrated. The subsequent fate was that of absorption of the necrotic tissue and replacement by new bone. This process in the two types of

graft seems to differ only in respect to the influence played by the variance in architecture. Spongy bone (the rib) is much more cellular and much more porous. In consequence, it is presumably more permeable to nutrient bearing body fluids, and cellular proliferation occurs earlier and progresses more rapidly. For the same reason osteoclasis, invasion by granulation tissue and new bone formation appear earlier and up to a certain point advance more rapidly. Beyond this point resorption greatly exceeds replacement. In the dense bone of tibial transplants the two processes maintained a more nearly balanced equilibrium throughout.
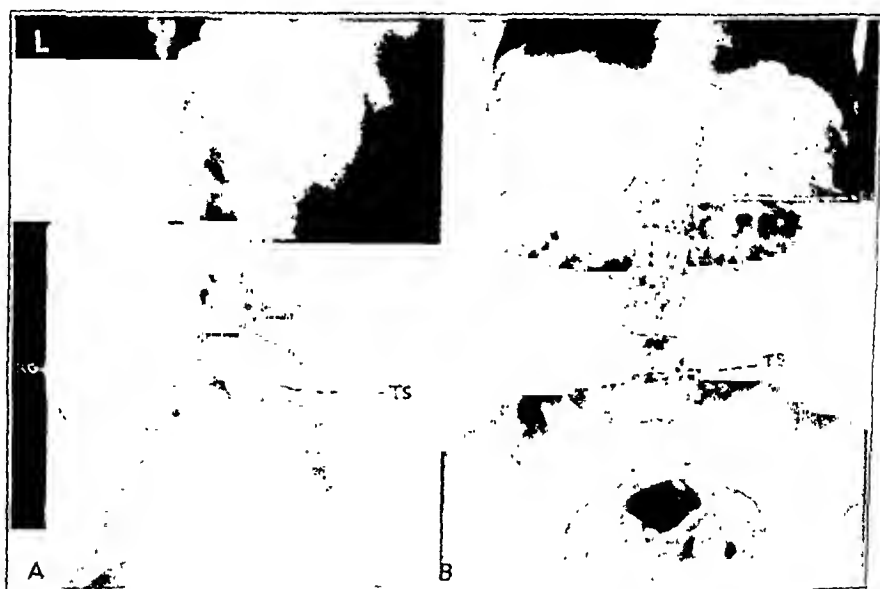
Fig. 9.—*A*, tuberculous spondylitis (*TS*) involving the bodies of the fourth and fifth lumbar segments. *RG* represents the span of fusion and rib grafts; *NB*, new bone deposit. *B*, note the calcified tuberculous lymph nodes and foci in the region of the spleen. *RB* indicates stumps of resected rib segments.

CASE REPORTS

The subsequent clinical deductions are based on a study in which rib grafts were transplanted to the spine, as illustrated in figure 8. This operation differs from that described by Allison [15] only in the use of rib grafts in place of osteoperiosteal transplants from the tibia, and from that referred to by Kleinberg [6] in the immediate transplantation of fresh grafts. It is essentially the Hibbs operation, with the additional support, the impetus to osteogenesis and the greater surety of a massive firm fusion to be gained from the engrafting of bone.

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15. Allison, N.: Fusion of the Spinal Column, Surg., Gynec. & Obst. **46**:826, 1928.
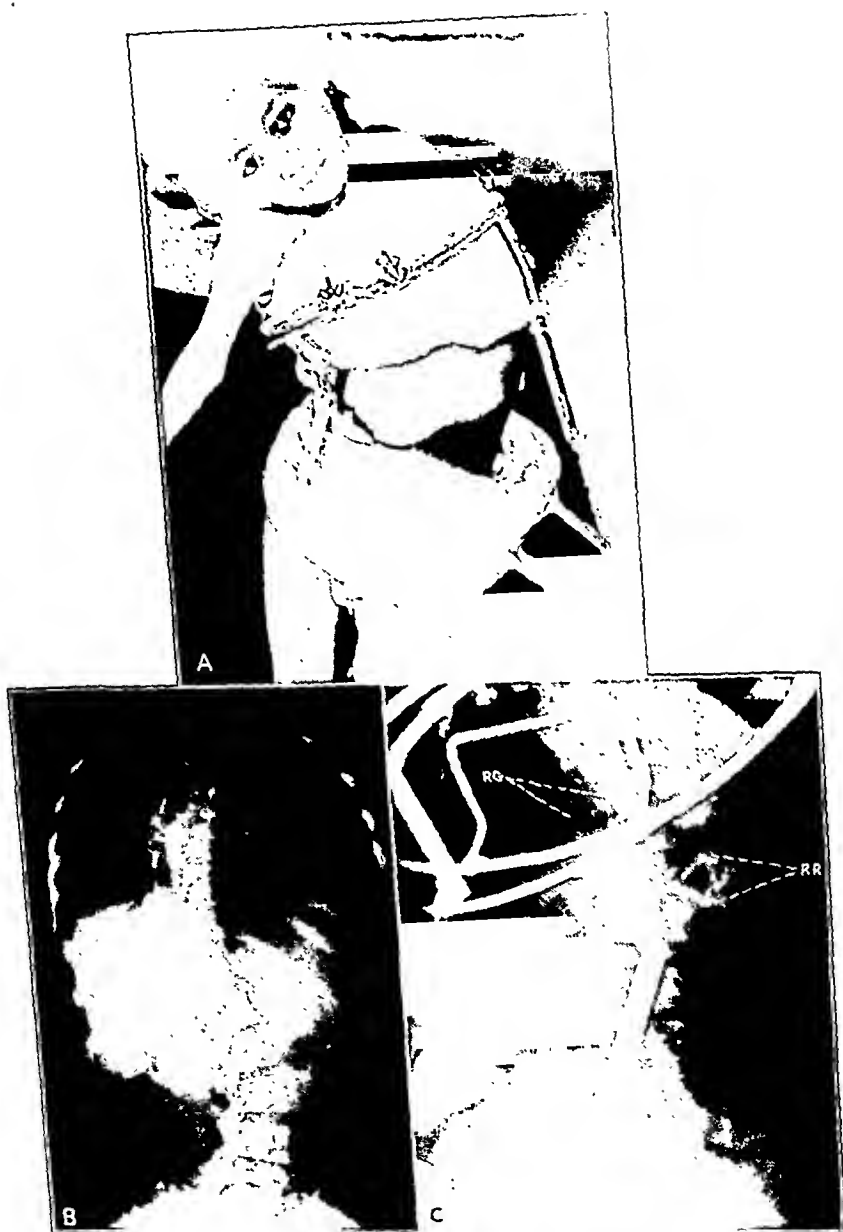
Fig. 10.—*A*, a patient with idiopathic scoliosis receiving correction of the spinal curvature in a modified (Risser), hinged, turnbuckle jacket. *B*, roentgenogram of the spine of the patient in *A* before correction and fusion. *C*, roentgenogram of the same patient after correction and the second stage of spinal fusion. *RG* points to rib grafts and *RR* to stumps of resected rib segments (the tenth and eleventh segments). Turnbuckle correction was continued after operation. Note the almost complete correction of the spinal curvature.

The ages of the twelve patients varied from 2 to 24 years, and the areas of the spine fused ranged from the sacrum to the second thoracic vertebra, inclusive. The group was composed of four cases of vertebral tuberculosis (figs. 9 to 12) and eight cases of scoliosis (figs. 10 *A* and *B* and 11 *A*). The latter series may be subdivided in regard to etiology into idiopathic, three cases; ricketic, one case; paralytic (anterior poliomyelitis), two cases, and congenital vertebral deformation, two cases. The two patients with congenital deformities of the spine were operated on by Dr. Compere,[16] and the fusion operations were supplemented by the removal of deformed vertebral bodies (two in one of the cases and one in the other).

Fig. 11.—*A*, ricketic scoliosis before correction and fusion. *B*, after correction and spinal fusion in two stages. *RG* points to shadow of rib graft and *RR* to stumps of resected rib segments. Note the regeneration of the ribs on the left side and the marked correction of the curvature.

The rib transplants consisted of segments from 14 to 22 cm. in length removed from two or more ribs, in most instances from the tenth and eleventh or from the eleventh and twelfth. In one case of scoliosis with a rather marked posterior bulge of the thoracic cage, the rib segments were resected from the center of that area to decrease the deformity by flattening the bulge.

In all cases a solid bony fusion was demonstrable clinically and by roentgen examination within three months after operation.

16. Compere, E. L.: Excision of Hemivertebrae for Correction of Congenital Scoliosis, J. Bone & Joint Surg. **14**:555 (July) 1932.

The advantages of rib grafts for general use have been outlined by Eloesser:

1. No special instrumentarium such as a motor-driven saw is required.

2. The rib is more workable than dense cortical bone; it can be bent and cut more readily.

3. The supply is practically unlimited, and the removal of segments of two or three ribs does not affect the well-being of the patient.
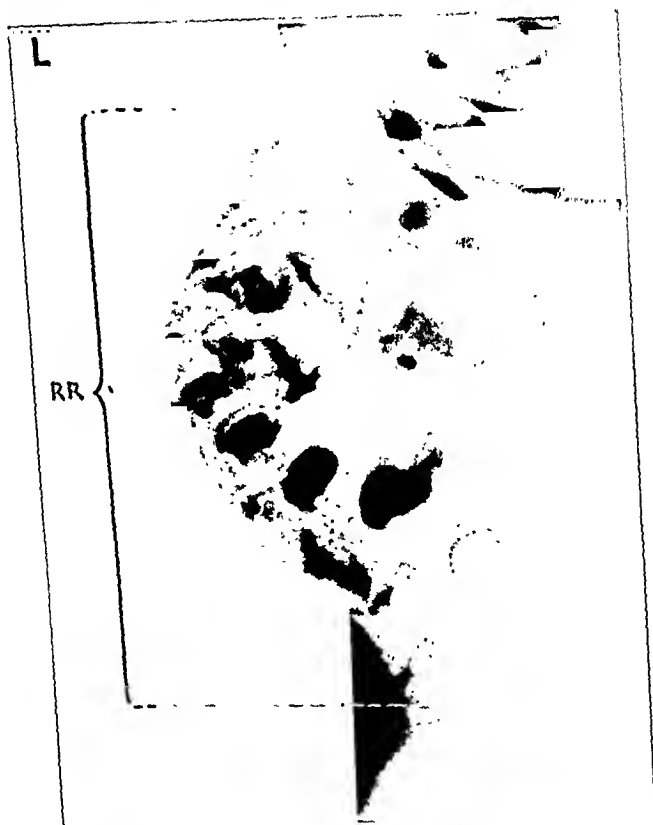
Fig. 12.—Extensive vertebral tuberculosis. Note the shadows of the rib transplants. *RR* marks the extent of fusion and of grafts.

4. The rib resection is neither more difficult nor more dangerous (with due caution to avoid injury to the pleura), nor does it require more time than the removal of a graft from the tibia.

In respect to their use for spinal implantation, the following advantages may be added:

1. The grafts are accessible in the same general field of operation.

2. The curve of the rib at its angle frequently is well adapted to the contour of the spine in cases of kyphosis or scoliosis.

3. There appears to be less shock than that associated with the removal of a tibial graft.

4. The grafts offer an alternative in certain cases in which tibial grafts are not available, owing to associated infection or fractures of the tibiae or loss of the lower extremities, or under circumstances in which a scar of the leg would be greatly objected to.

5. As described by Whitman, the resection of ribs may serve a dual function in cases of scoliosis with rotation deformities of the chest.

SUMMARY AND CONCLUSIONS

1. Both clinical and experimental comparative studies of costal and tibial bone grafts are reported. These studies relate particularly to quantitative osteogenesis of the two types of bone represented, with reference to clinical application in spinal fusion operations. Ribs undergo revascularization and absorption and are replaced by new bone much more rapidly and extensively than dense bone. When no great demand is made on the inherent strength of the graft, as in the type of operation illustrated, ribs serve the purpose of transplanted bone as satisfactorily as do full thickness tibial grafts and probably more effectively than thin osteoperiosteal transplants. Likewise, certain advantages of minor significance are pointed out.

2. Some evidence in support of the cellular theory of osteogenesis is presented. That all transplanted bone does not die is demonstrated by the survival of cells in lacunae encased in bone in two of the six specimens from human beings recovered twelve and fourteen days, respectively, after transplantation. The early and heavy deposits of new bone on the surface overlying these living bone cells suggest a definite osteogenic interrelationship.

LYMPHOBLASTOMAS OF THE GASTRO-INTESTINAL TRACT

THEODORE S. RAIFORD, M.D.

BALTIMORE

Lymphoid tumors of the gastro-intestinal tract are by no means rare and have been treated at length in the literature of the past three decades. The majority have been included in the more or less general term of sarcoma, but while such a classification is no doubt correct, the lymphoid tumors form a group in themselves and should be considered separately. The histogenesis of this group is still marked by obscurity and has been the basis for much controversial opinion. The nomenclature is confused, and owing to a lack of knowledge of the histogenesis of these tumors, they have run the gamut of pathologic classification.

More important than a suitable nomenclature is the recognition of a malignant process. Some of the tumors undoubtedly are malignant. They metastasize and recur after excision. Others pursue the course of a benign growth, and it is frequently impossible to differentiate the two types microscopically.

The problem confronting the pathologist is twofold, first to form a suitable working classification and second to recognize the grade of malignancy. For this purpose a study has been made of 45 cases occurring in the Surgical Pathological Laboratory of the Johns Hopkins Hospital.

HISTORICAL DATA

Most of the literature on intestinal sarcomas has appeared during the past forty years. In 1883, Debrunner[1] described one of the earliest authentic cases occurring in the large bowel. Pick's[2] case was reported the following year. Pitt[3] was able, in 1889, to gather reports of 18 cases from the literature and added 1 case of his own, but he classified them all as lymphadenomas. Orth,[4] in an inaugural thesis, one year later, gave abstracts of 11 cases of sarcoma of the intestines, which were about evenly distributed between the small intestine, the colon and

1. Debrunner, A.: Inaug. Diss., Zurich, 1883.
2. Pick, E.: Prag. med. Wchnschr. 9:96, 1884.
3. Pitt, G. N.: Tr. Path. Soc., London 40:80, 1889; Rev. gén. de clin. et de thérap. 44:380, 1930.
4. Orth, L.: Inaug. Diss., Heidelberg, 1890.

the rectum. Baltzer's [5] comprehensive review of the subject appeared in 1892. He covered the subject in detail and commented on the predilection of lymphoid tumors for the small intestine. Libman's [6] article published in 1900 was no doubt the best review to that date and contained a list of all cases reported to that time, totaling 59. Crowther [7] reviewed the literature again in 1913 and compiled statistics on 122 cases. In 1919, Graves [8] extended this number to 249.[9] The work of Liu,[10] published from this laboratory, while brief, is the latest comprehensive survey.

Although lymphoid tumors have been the object of much discussion, most pathologists admit an inadequacy of knowledge dealing with classification, diagnosis, pathogenesis and prognosis. As a result, most of the cases are reported in the literature under a variety of names. Sarcoma is perhaps an all inclusive term; certainly most of this group of tumors have fallen originally into that classification. The name implies a definite malignant process, however, and cannot be applied to certain tumors which show no malignant characteristics. Neither can the name infectious granuloma or chronic inflammatory tumor be applied with impunity to a tumor every feature of which supports the impression of a high grade of malignancy. Graves, noting its ambiguity, made a plea for uniformity of nomenclature. He suggested the term lymphoblastoma, which, according to Mallory,[11] means "a tumor of mesenchymal origin, the cells of which would normally tend to differentiate into cells of the lymphocytic series." Such terms as "round cell sarcoma" are no doubt correct, but indicate little more than the morphology of the cells. The name "chronic inflammatory tumor" tells nothing of the morphology and is misleading from the standpoint of histogenesis. Considering the group in its various phases, it has seemed preferable to adopt Graves' term for the purpose of unification.

LOCATION

In view of the increasing number of cases appearing in the literature, it would be a difficult task to attempt a summary of all reported cases of lymphoblastomas of the gastro-intestinal tract. The 45 cases occur-

5. Baltzer, A.: Arch. f. klin. Chir. **44**:717, 1892.

6. Libman, E.: Am. J. M. Sc. **120**:309, 1900; **129**:813, 1905.

7. Crowther, C.: Clin. chir. **21**:2107, 1913.

8. Graves, S.: J. M. Research **40**:415, 1919.

9. These reports include only tumors of the small intestine and ileocecal region, and exclude those of the stomach and large intestine.

10. Liu, J. H.: Tumors of the Small Intestine with Especial Reference to the Lymphoid Cell Tumors, Arch. Surg. **11**:602 (Oct.) 1925.

11. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914; J. M. Research **13**:113, 1904-1905; J. Exper. Med. **10**:575, 1908.

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4. Orth, L.: Inaug. Diss., Heidelberg, 1890.

CLINICAL OBSERVATIONS

The clinical manifestations of lymphoblastomas are not unlike those brought on by any malignant process in the gastro-intestinal tract.

The general symptoms are malaise, cachexia, loss of weight, weakness and secondary anemia. Some authors point out the greater severity of these symptoms in lymphoblastoma than in carcinoma and attempt to differentiate the two conditions on this basis. Attention was called to the absence or late appearance of obstruction by Treves and Baltzer.[5] This is regarded as a diagnostic point by Williams,[12] Haggard[13] and others. While it is true that general symptoms are usually present before obstruction develops, this fact cannot be regarded as an infallible sign in view of its inconstancy in lymphoblastomas and its occasional occurrence in carcinomas. Pain is a fairly constant symptom, but is of
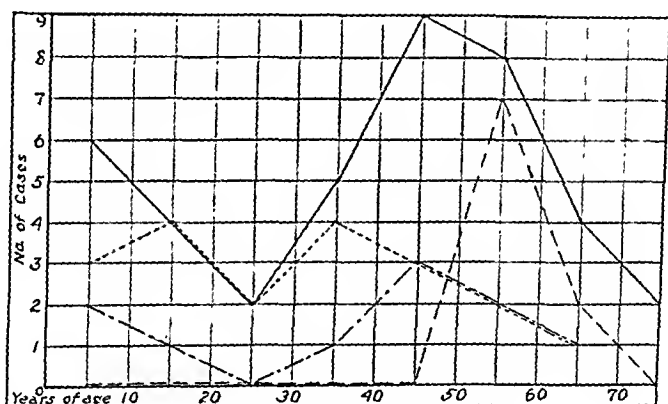
Fig. 1.—Graph representing the age incidence for tumors in various parts of the gastro-intestinal tract. The solid line represents the entire group; the dash line, the stomach; the dot line, the small intestine, and the dash and dot line, the large intestine. Note the difference between the age incidence for tumors occurring in the small intestine and that for those occurring in the stomach.

a dull, aching type in contradistinction to the sharp and cutting variety characteristic of acute obstruction. Even this, however, is frequently delayed for some time after the beginning of the tumor, and on account of the absence of symptoms, the tumor may go unrecognized for months.

Nausea and vomiting are usually present at some time in the course of the disease, but are not marked, and the clinician may be at a loss to explain their presence in the absence of other indicative signs. Distention rarely occurs early in the disease, but the patient may complain of vague abdominal distress and attacks of indigestion.

12. Williams, E. M.: New Orleans M. & S. J. **66**:173, 1913-1914.

13. Haggard, W. D.: Tumors of the Small Intestine, J. A. M. A. **59**:253 (July 27) 1912.

There is nothing characteristic about the stools. Some patients complain of marked constipation; others, of diarrhea, but most commonly of alternating attacks of constipation and diarrhea. Melena is not a frequent occurrence.

Laboratory findings reveal varying degrees of secondary anemia and a moderate leukocytosis. The stools may or may not contain occult blood.

A slight rise in temperature in the afternoon (from 99 to 100 F.) is a more or less constant feature and is partially responsible for the infectious theory of the origin of the tumor. The presence of fever with sarcoma has been recognized for several years, and many early papers call attention to it as distinctive. Williams[12] suggested the resorption of a toxic material from necrotic areas as a possible explanation, but this theory is without proof. An indirect effect of the tumor on the body metabolism is more plausible.

Roentgen findings may show a filling defect in the stomach or the large intestine or a dilatation of the proximal bowel if obstruction is present. If the tumor is in the small bowel, roentgenograms are of less value, owing to the difficulties of localization and of obtaining a homogeneous distribution of barium throughout the intestine. In rare instances, a bulbous shadow may be present owing to the dilated form of the tumor. When negative, the roentgen findings do not rule out a tumor, and when positive, it is impossible to localize in the majority of cases.

Intussusception is a frequent complicating condition and is responsible for a characteristic clinical syndrome. The onset is marked by the acute pain of intestinal obstruction with vomiting, distention, tympanites and obstipation. A sausage-shaped tumor is frequently palpated, usually in one or the other flank. A few bowel movements containing bloody mucus may occur immediately following the intussusception, but soon cease altogether. The condition is symptomatically identical with the spontaneous intussusception occurring in infants, but does not reduce itself. Kasemeyer[14] stated that 10 per cent of 284 cases of intussusception reviewed by him were caused by sarcomas. The condition is frequently found at the ileocecal valve, resulting in an ileocolic invagination, and is due partly to the ease with which this part of the bowel invaginates, and partly to the frequency of lymphoblastomas in this region.

DIAGNOSIS FROM CARCINOMA

While it is not attempted to differentiate lymphoblastomas from carcinomas on the bases of clinical data alone, the characteristic features

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14. Kasemeyer, E.: Deutsche Ztschr. f. Chir. **118**:205, 1912.

of each as derived from personal observation and from the literature are as follows:

	Lymphoblastoma	Carcinoma
Age:	Young. Patients are usually in first four decades. May occur in infants	Attacks persons of the "cancer age" in the fifth and sixth decades
Location:	Most common in lower part of the ileum and cecum	Most common in stomach and rectum
Course of Disease:	Rapid	Prolonged
Pain:	Dull and aching, occurring late in disease	Sharp and cutting following distention and coincident obstruction
Obstruction:	Occurs late or not at all	Commonly found
Laboratory Findings:	Blood in stools rare. Rise in temperature in afternoon present. Anemia severe	Blood in stools common. Rise in temperature in afternoon absent. Anemia moderate
Gross Form:	Large aneurysmal dilatation	Small annular constriction

These differences should be accepted with reservation, since probably no one tumor will show all of the characteristics. Nevertheless, when a majority are present, they may be extremely useful in differentiating the two conditions.

GROSS PATHOLOGIC CHANGES

Occurring so often that they cannot be considered accidental, lymphoblastomas produce dilatation rather than constriction of the intestine. This characteristic has drawn the comment of many investigators. Williams,[12] Jopson and White,[15] Nothnagel [16] and others regarded it as typical. A popular explanation of the phenomenon is the invasion of the muscular coats with paralysis and subsequent dilatation. Another theory is that of origin in the submucosa followed by subsequent infiltration and extension through the planes of least resistance. The tumor frequently resembles a hollow sphere with a moderate degree of constriction at either end, where the lumen of the intestine enters and leaves the tumor (fig. 2). This, however, occurs chiefly in the small intestine. In the stomach and large bowel the form is more apt to be pedunculated or sessile (figs. 3 and 4). Fletcher [17] described a case with multiple plaques arising from the aggregate nodules in the terminal ileum. Brettauer's [18] patient had multiple hard white nodules in the cecum.

The tumor is white, and its consistency is firm and rubbery. The cut section has a translucent sheen. The mucosa is usually intact over the tumor unless the tumor growth has impaired the circulation and caused devitalization. Areas of central necrosis are sometimes seen, and sterile, purulent fluid with necrotic tumor tissue is evacuated. The

15. Jopson, J. H., and White, C. Y.: Am. J. M. Sc. **122**:807 1901.

16. Nothnagel, H.: Diseases of the Intestines and Peritoneum, Philadelphia, W. B. Saunders Company, 1904, p. 460.

17. Fletcher, W.: Practitioner **83**:374, 1909.

18. Brettauer, Joseph: Am. J. Obst. & Gynec. **76**:90, 1917.

Fig. 2.—Gross photograph of a lymphoblastoma of the ileum, illustrating the typical aneurysmal dilatation characteristic of lymphoblastoma (Path. no. 41291). The tumor surrounded the lumen of the intestine and produced a dilatation, rather than the stenosis characteristic of carcinoma. This was a malignant reticuloma. It was removed at operation, but the patient died three months later of metastases.
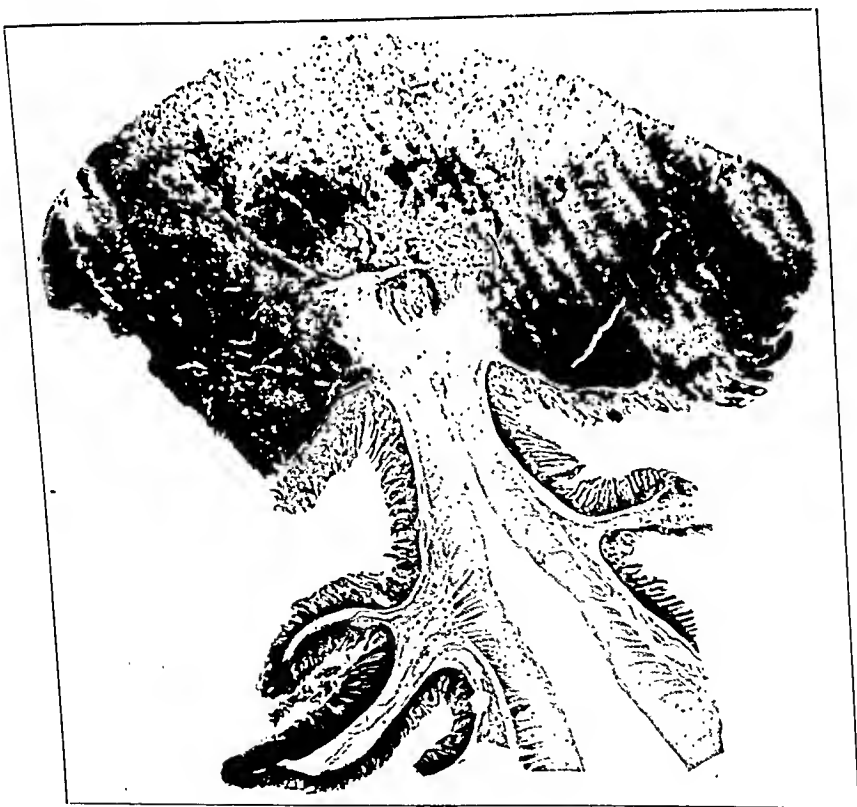
Fig. 3.—Photograph of a section through a polypoid lymphoblastoma (Path. no. 16485). This was one of six polyps occurring in the upper part of the jejunum. It had produced an intussusception. The intussuscepted bowel was removed at operation together with a portion of the bowel containing the remaining tumors. Convalescence was uneventful, and the patient is entirely well. This was a malignant lymphocytoma.

fluid may be so predominant at times as to cause the tumor to be mistaken for an abscess.

The size varies greatly. As a rule, on account of the peculiar form of the aneurysmal dilatation, the tumors attain a much larger size than carcinomas, and it is not at all uncommon to see a tumor the size of a grapefruit.

MICROSCOPIC PATHOLOGIC CHANGES

The histologic anatomy of the lymphoblastomas is typified by dense accumulations of closely packed cells with a stroma of varying abundance. The tumor is usually located in the submucosa and does not involve the mucosa which passes intact over the surface. The direction assumed by the tumor in its growth is usually parallel to the intestine. It seeks the planes of least resistance, and produces a flattened tumor. In advanced stages, especially of tumors of a malignant
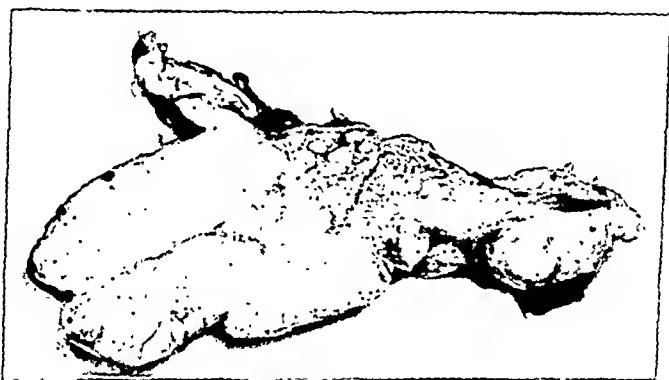
Fig. 4.—Photograph of a pedunculated lymphoblastoma arising in the cecum near the ileocecal valve (Path. no. 29605). It had produced an ileocolic intussusception. The right half of the colon was removed, and a lateral ileocolostomy was performed. This was a malignant lymphocytoma. The patient recovered and is well.

nature, the muscularis is invaded or infiltrated. In some instances the vascularity is increased, but in the majority it is impaired and the vessel walls are invaded by the tumor. An admixture of leukocytes, plasma cells and mononuclear cells is commonly seen. There is a surprising predominance of eosinophils. The tumor cells themselves vary somewhat with the type most commonly found in the intestinal tract.

Benign Lymphocytoma.—This is the benign type of tumor commonly thought to be of infectious origin, but the etiology of which is sometimes obscure. The cells comprising the tumor are of the small, lymphocytic variety (fig. 5). They are round and contain a dark-staining nucleus and a minimal amount of cytoplasm. They are not dispersed homogeneously throughout the tumor, but may be sparse in some parts and densely packed in others. The extension of the tumor is of a benign nature, the cells infiltrating between the normal elements without giving

the picture of malignant destruction. Plasma cells may be abundant. The stroma is scant in some places, but in others there may be a dense fibrous reaction with hypertrophy of the connective tissue. When the fibrosis is marked and large giant cells of the Dorothy Reid type are present, it is suggestive of intestinal Hodgkin's disease, although the occurrence of this entity is still a matter of doubt. If the cells have a
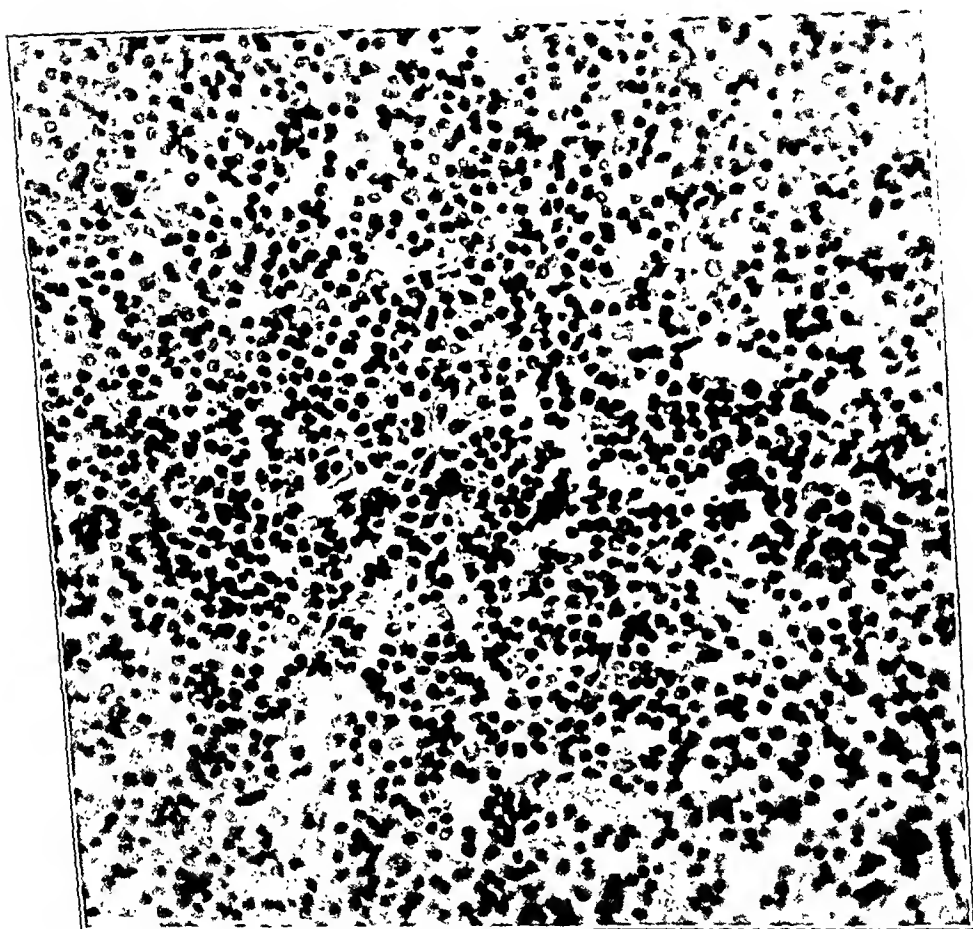
Fig. 5.—Low power photomicrograph of a nonspecific granuloma in the stomach (Path. no. 44757). Note the uniformity of size of the lymphocytic cells, the absence of reticulum and the irregular disposition of the cells between the stroma of the wall of the stomach.

predilection for perivascular arrangement, syphilis may be suspected. The presence of tubercles and characteristic giant cells is indicative of tuberculosis. Occasionally the intestinal tumor may be part of a generalized process such as lymphatic leukemia. When none of these characteristics are present, the tumor is left in the rather loose classi-

fication of nonspecific granuloma, comprising a heterogeneous group sometimes indistinguishable from tumors of a malignant nature.

Malignant Lymphocytoma.—This group of lymphoblastomas differs from the preceding both in the character of its cells and in the
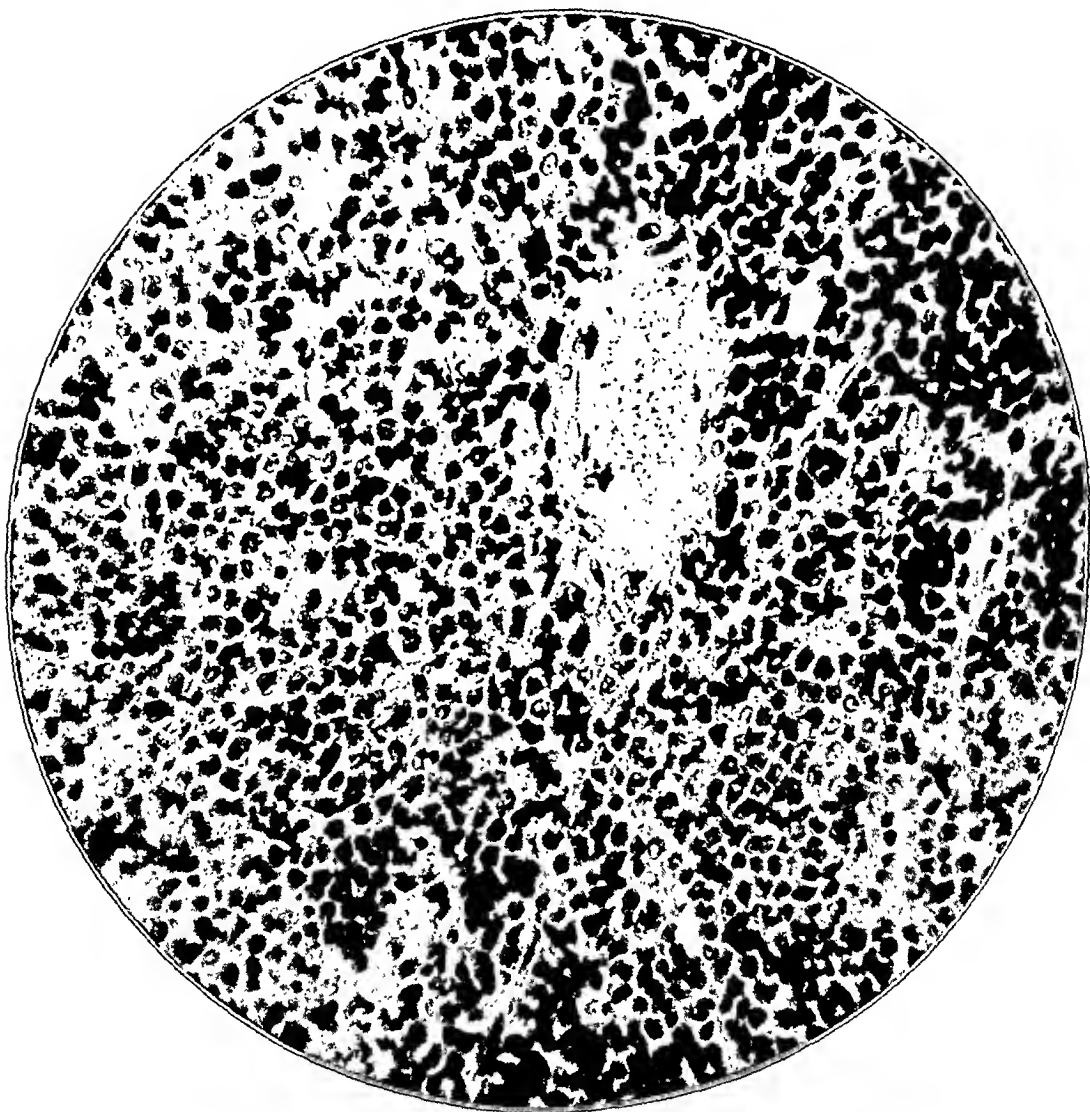
Fig. 6.—Low power photomicrograph of the tumor shown in figure 4 (Path. no. 29605). Note the closely packed accumulations of round cells, which are larger than normal lymphocytes. They are invading the tissue profusely, but have not encroached on the lumen of the blood vessel in the center of the picture.

manner of its growth. The majority of the cells are slightly larger than normal lymphocytes. They are uniformly round, with scanty cytoplasm. The nucleus stains much lighter and contains numerous chromatin particles which have a tendency toward central arrangement.

One or more nucleoli may be seen (fig. 8). Cells resembling normal lymphocytes may also be present, and between these two forms, one may find cells representing all stages of transition from normal lymphocytes to tumor cells.

The tumor cells are packed closely together and form a dense homogeneous mass which does not, however, destroy the normal archi-
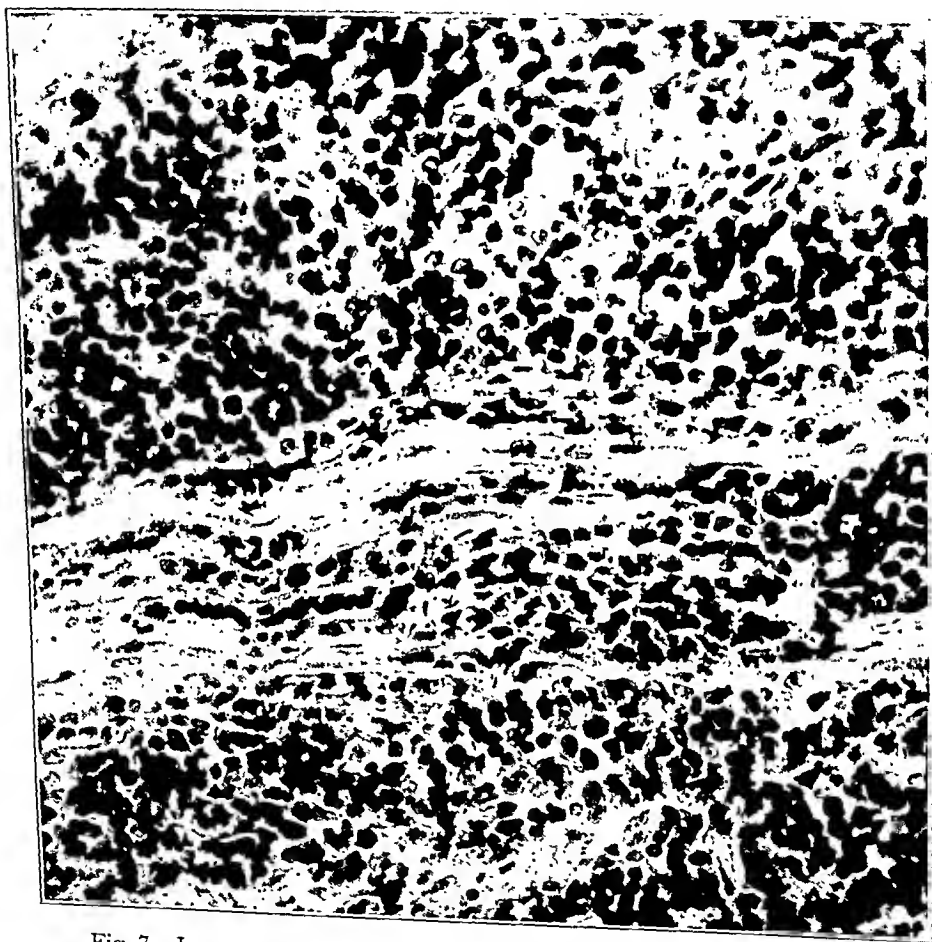
Fig. 7.—Low power photomicrograph of a malignant lymphocytoma of the colon (Path. no. 28312). The cells are similar to those described in the preceding photograph and are infiltrating between the connective tissue fibers of the intestinal wall without destroying them.

tecture of the intestinal wall (fig. 7). Instead, they are packed between the muscle and connective tissue fibers and apparently follow the lines of least resistance. Vascularity is not marked, and the capillaries present are not invaded by the tumor cell (fig. 6).

Giant cells are rarely if ever seen. Eosinophils are common, and small plasma cells are abundant.

Benign Reticuloma.—This type is not a true tumor formation, but is analogous to the hyperplastic lymphadenitis common in the presence of either an infectious process or a malignant condition of the bowel. It typifies the enlarged, hard mesenteric gland frequently mistaken at operation for metastatic carcinoma.

On section one finds not the malignant cells of the neoplasm, but a hyperplasia of the reticulum cells of the primordial follicles and lymph sinuses (fig. 9). The cells are large and polygonal and possess a moderate amount of cytoplasm and a dark-staining nucleus. There are
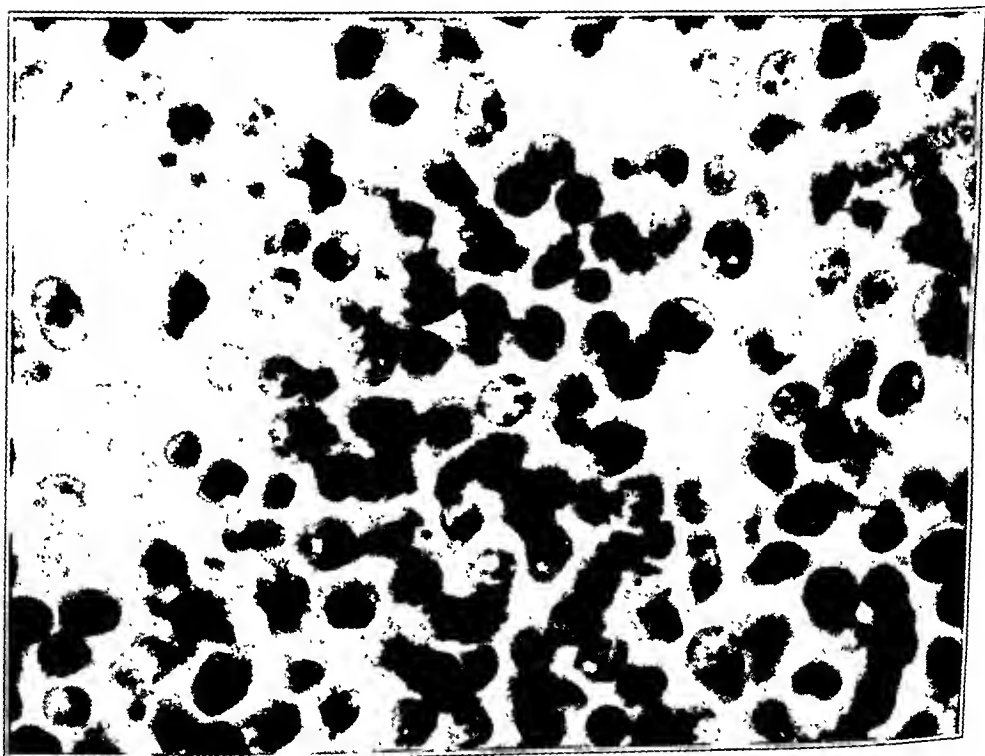
Fig. 8.—High power photomicrograph of a malignant lymphocytoma of the colon (Path. no. 28312). (From the same case as fig. 7.) Note the regularity of the cell structure both in size and in staining reaction. There are smaller cells which are normal lymphocytes between this type and the larger cells. All stages of transitional growth may be observed.

many other cells resembling endothelial cells which are larger and take a lighter stain, the nuclei of which contain numerous chromatin particles. Reticulum is abundant and forms a loose, supporting stroma for the cells. This is apparently a normal stimulatory response, and while it perhaps has no place in a consideration of neoplastic growth, it should be included as the benign counterpart of the malignant reticuloma in the following group.

Malignant Reticuloma.—These are the tumors thought to arise from the reticulum cells of the primordial follicles of the lymph nodes. The

cells are large and show an active state of proliferation (fig. 10). The nuclei are large and round or oval, and contain a large number of chromatin particles, which are most frequently concentrated at the periphery. Nevertheless, the nucleus is light-staining and has the appearance of being malignant (fig. 12). The cytoplasm is moderate in amount and polyhedral in shape, and frequently exhibits sharp, "pig-tail" corners.
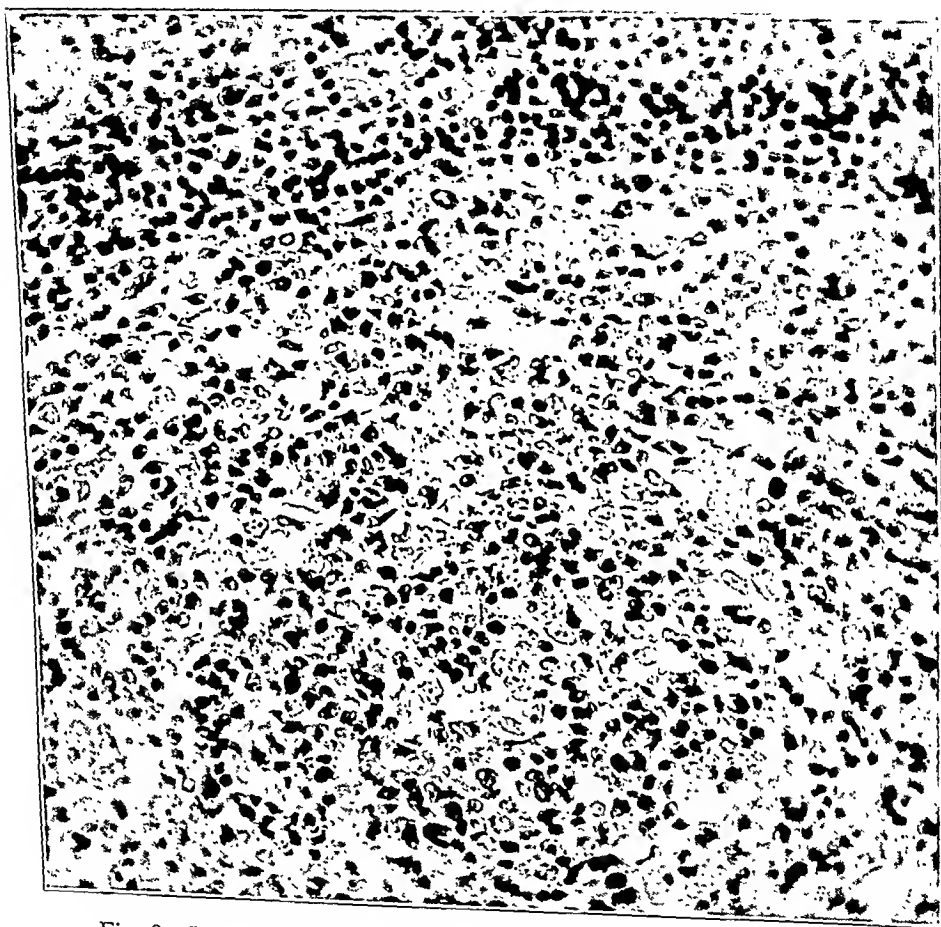
Fig. 9.—Low power photomicrograph of a lymph gland removed at operation for carcinoma of the stomach (Path. no. 41307). It was enlarged and hard and was thought to be involved by metastatic growth. Microscopic examination, however, showed a hyperplastic lymphadenitis, involving the germinal centers. There was no evidence of a malignant process in the section. Note the similarity of these cells to those in figure 10. The cells are large and polygonal, and are not closely packed. They are supported loosely by a moderate amount of reticulum. Larger endothelioid cells may also be seen. The germinal center is surrounded by normal lymphocytes. This is a benign reticuloma.

Reticulum is present but varies in amount with the portion of the tumor. In some areas it is abundant; in others, almost negligible. The cells are not packed closely together and invade the normal structures with every characteristic of malignant growth.

A peculiarity of some of these tumors is the presence of large giant cells (fig. 11). These may be of two types. One contains two or more nuclei, similar to those of the single tumor cells, and gives the impres-

Fig. 10.—Medium power photomicrograph of a malignant reticuloma of the ileum (Path. no. 41291). (From the same case as fig. 2.) Note the large, irregular cells with the "pig-tail" cytoplasm and the reticulum. The cells are not as closely packed as in malignant lymphocytoma.

sion of a cellular fusion. The other is a large cell with a single nucleus, much larger than that of the tumor cell. This nucleus is light-staining and contains less chromatin, but one or two nucleoli. The cytoplasm is darker than the nucleus. Flexner[19] and Libman[6] have called attention to these, suggesting that they may be of parasitic origin and connected with the etiology of the growth.

19. Flexner, S.: Rep. Johns Hopkins Hosp. **3**:153, 1893.

Vascularity is well developed in this type of tumor. Numerous capillaries can be seen, most of which have been invaded by the tumor cells.

An infiltration of small round cells is usually found. This consists of small lymphocytes and plasma cells. Polymorphonuclear leukocytes may be present, especially if secondary infection has taken place. An
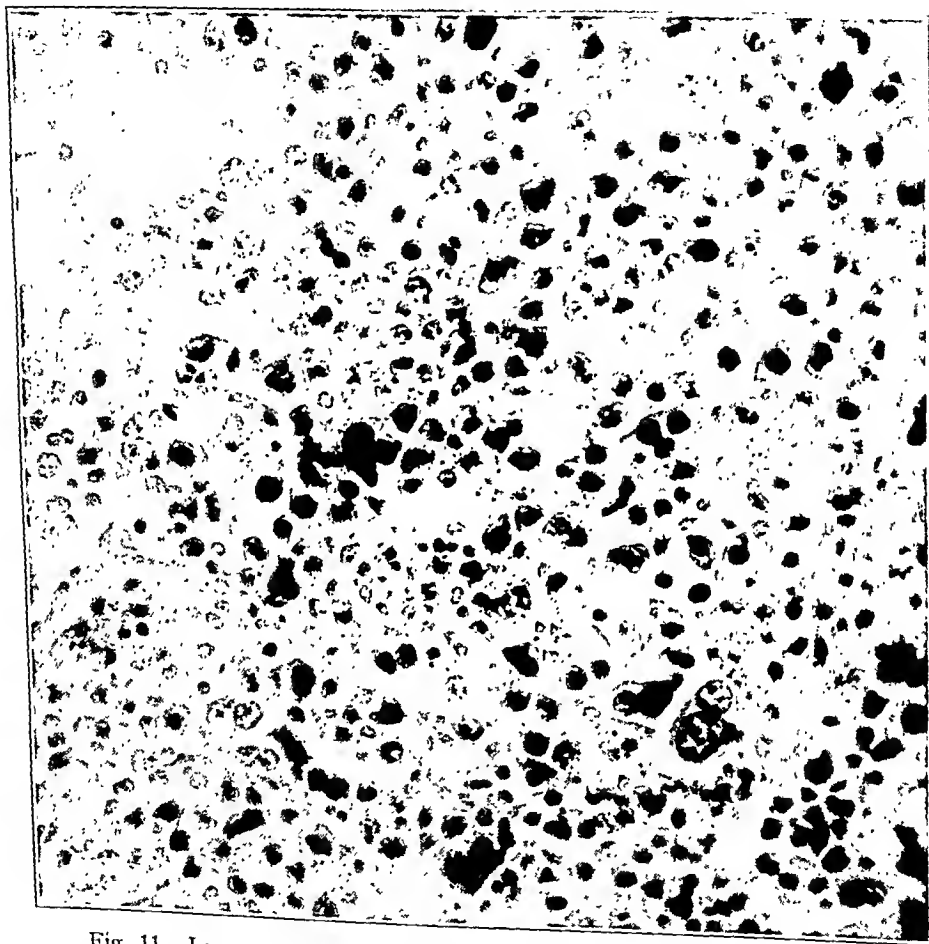
Fig. 11.—Low power photomicrograph of a malignant reticuloma of the colon (Path. no. 32293). This area shows, in addition to the irregular malignant cells pointed out in the preceding photograph, large giant cells which contain two or more nuclei and resemble very much the tumor giant cells found in sarcoma. Eosinophils are present, but cannot be distinguished without their characteristic red granules.

apparent characteristic of the tumor is the presence of numerous eosinophils. This is, of course, more marked in some tumors than in others, but is a fairly constant finding.

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19. Flexner, S.: Rep. Johns Hopkins Hosp. **3**:153, 1893.

While an intricate classification is ambiguous and superfluous, the lymphoblastomas should be further classified to give a satisfactory working knowledge. Ewing classified the tumors arising from lymphoid tissue as follows:

Origin	Anatomic Type	Clinical Type
Lymphocytes:	Lymphocytoma	Simple lymphoma, Tuberculous lymphoma, Lymphatic leukemia, Pseudo-leukemia
Reticulum Cells:	Large round cell hyperplasia or neoplasia	Granuloma malignum, Myeloid leukemia, Hodgkin's sarcoma
Endothelial Cells:	Endothelial hyperplasia or neoplasia	Large cell sarcoma, Endothelial hyperplasia of tuberculosis, etc. Endothelioma

The tumors of lymphocytic origin that have been dealt with are therefore lymphocytomas and may be roughly classified benign and malignant. Those of reticulum cell origin may be similarly classed as reticulomas and are likewise benign and malignant.

Benign Lymphocytoma.—Tumors of this group comprise those commonly known as chronic inflammatory tumors, benign granulomas and the intestinal manifestations of certain specific infections such as tuberculosis and syphilis. The tumor cells usually represent a cellular reaction to stimulation of an inflammatory nature.

Malignant Lymphocytoma.—This is the tumor commonly diagnosed small round cell sarcoma. It is a true neoplasm of the lymphocytic cells and possesses all the characteristics of a malignant process, pursuing a progressive course and terminating fatally in the absence of successful intervention. Metastases may occur, but owing to the similarity of the cells to normal lymphocytes, they are frequently overlooked.

Benign Reticuloma.—This is not a true neoplasm but should be included as representative of the benign reticulum cell hyperplasia. Enlarged mesenteric glands are not infrequently found in many conditions. They are especially common in the presence of carcinoma of the bowel, and for this reason are frequently diagnosed as metastases until proved otherwise by histologic examination. It is then found that there is a hyperplasia of the reticulum cells of the lymph node bearing a striking resemblance to certain types of sarcoma.

Malignant Reticuloma.—This type of the reticulum cell sarcoma is apparently a malignant neoplasia of the reticulum cells of the follicles and sinuses. The cells undergo malignant metamorphosis, grow rapidly and metastasize early. No satisfactory explanation has been offered for the presence of the giant cells alluded to in a foregoing paragraph. The parasitic theory of Flexner and Libman is unique, but evidence in support of such a theory is lacking. The eosinophilia is likewise difficult to understand and is a characteristic for which there is no apparent explanation.

MALIGNANCY

The malignancy of the lymphoblastomas is still a debated question. The problem presumably arises from the difficulty experienced by the pathologist in differentiating the benign from the malignant by the use of the microscope. Undoubtedly there are tumors which are benign, and it may be said in defense of the pathologist that from the microscopic picture alone it is difficult to establish the grade of malignancy. Clinical data and the progress of the disease are no more helpful. It should not, however, in view of the characteristics previously mentioned, be difficult to distinguish the lymphocytoma from the reticuloma group.
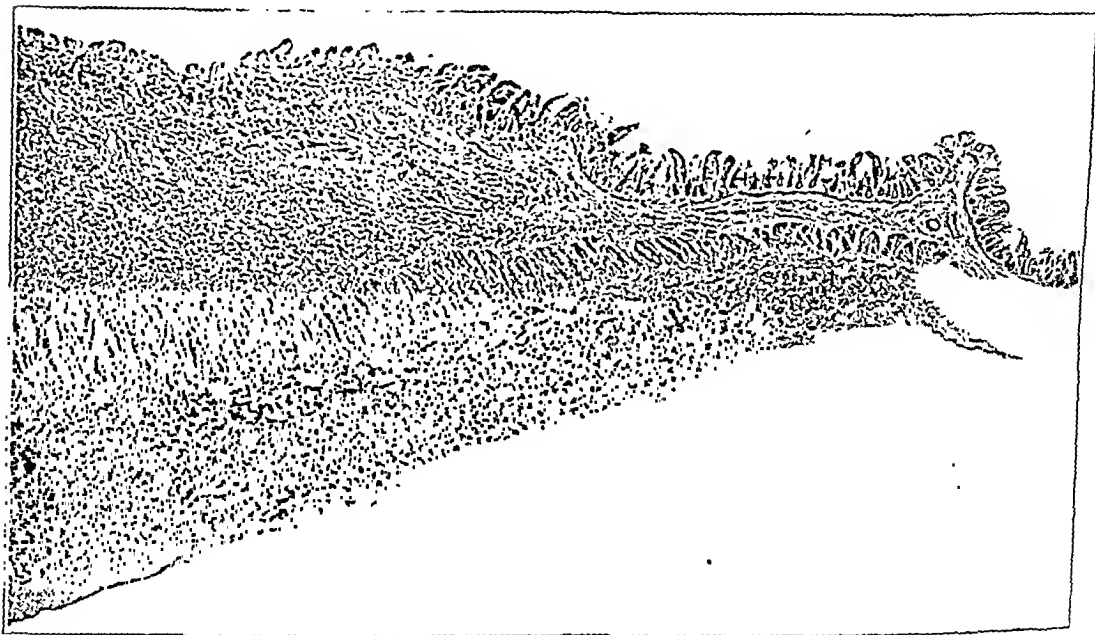
Fig. 13.—Low power photomicrograph of a malignant lymphocytoma developing in a Peyer's patch in the lower part of the ileum (Path. no. 7403). Under high power one can see the remains of normal lymphoid tissue. This tumor was growing in a flat plaque, producing a flattened, oval elevation in the wall of the intestine.

Lymphoblastomas are commonly thought to have a poorer prognosis than carcinomas. This is not wholly true, but varies with the type of tumor. The reticulomas are without doubt more malignant than the lymphocytomas and represent a grade of malignancy comparable to grade IV adenocarcinomas. The lymphocytomas, on the other hand, metastasize late, if at all, and correspond to adenocarcinomas of grades I and II in their manifestations of malignancy.

The fact remains that microscopic differentiation of the benign from the malignant is difficult and frequently impossible. In the light of

present knowledge, however, they must all be regarded as potentially malignant.

Since the lymphoblastomas rarely produce constriction in the early stages of the disease, the condition is not recognized until in its advanced stages. This is partially responsible for the grave prognosis usually associated with the tumor. If recognized early the ultimate mortality would no doubt be less than that of carcinoma. As it is, most of the tumors are diagnosed after they have attained a size sufficient to impair the successful extirpation, and the chances for ultimate recovery are correspondingly poor. In certain cases a superimposed condition such as intussusception may identify the tumor early and thereby enhance the recovery of the patient. One may say in summary, therefore, that, like carcinomas, the prognosis is good when the condition is recognized early and resection is performed. In addition, the factor of earlier metastasis in reticulomas, gives to these a graver prognosis, while lymphocytomas are more apt to be recognized before the condition is inoperable, and respond favorably to operative intervention.

TREATMENT

Surgical intervention offers the best chance of cure if the disease is recognized early. It is preferable to remove the section of intestine containing the tumor regardless of the size of the growth. The mortality attending resection is sufficiently low in competent hands to justify the operation, and although a tumor may appear perfectly benign in the gross, it is best to remove a good margin of healthy tissue. In the larger organs, such as the stomach and cecum, an excision is sometimes necessitated by the location. If this is the case, every effort should be made to remove as wide a margin of healthy tissue as possible. It is also well to remove adjacent glands with the tumor. It is extremely difficult to detect early glandular metastases even in histologic section, but, as has been pointed out, glandular enlargement is common. This in many cases is due to a simple lymphadenitis, but it is wiser to remove the metastases as extensively as possible with the tumor.

Irradiation has been used in a few inoperable cases with satisfactory results. Balfour and McCann [20] have emphasized the favorable result of radium and roentgen therapy, both as a preoperative measure and as a palliative treatment in inoperable cases. The tumors are radiosensitive to a certain degree, and although it cannot be hoped to bring about a complete cure, a temporary cessation of symptoms accompanied by a decrease in the size of the tumor may be expected.

20. Balfour, D. C., and McCann, J. C.: Am. J. Cancer 15:440, 1931.

TABLE 2.—*Lymphoblastomas of the Gastro-Intestinal Tract (15 Cases)*

Path. No.	Race	Sex	Age	Location	Duration	Chief Symptoms	Treatment	Gross Appearance	Microscopic Type	Result
41757	W	M	54	Stomach	8 mos.	Progressive weakness and loss of 30 pounds (13.6 Kg.)	Partial resection of stomach; anterior gastro-enterostomy	Thick nodular mass occupying greater curvature of stomach	Benign lymphocytoma	Dead, peritonitis
41177	W	F	51	Stomach	3 yrs.	Weakness; general glandular enlargement; loss of weight	No operation; autopsy specimen	Ulcerated mass in stomach with metastases to liver and regional glands	Malignant reticuloma	Dead, pneumonia
43525	W	M	50	Stomach	......	Palpable epigastric mass, subjectively increasing in size	Exploratory laparotomy for inoperable carcinoma of stomach; biopsy	Large lymph gland	Malignant reticuloma	Dead, metastases
37570	W	F	29	Stomach	3 wks.	Slight gastric upset with eructation and distention	Partial resection of stomach	Thick, ulcerated mass in wall of stomach	Malignant lymphocytoma	Lost
32582	W	M	62	Stomach	6 mos.	Belching, indigestion and loss of weight	Partial resection of stomach	Ulcerated mass in wall of stomach	Malignant lymphocytoma	Dead, postoperative embolus
28691	W	M	52	Stomach	18 mos.	Pain, belching, vomiting and distention	Partial resection of stomach	Large, thick ulcer	Malignant lymphocytoma	Dead, 1 year, recurrence
25018	C	M	55	Stomach	6 wks.	Vomiting; diarrhea	Partial resection with posterior gastro-enterostomy	Large, fungating ulcer, perforating	Malignant lymphocytoma	Dead, postoperative shock
15100	W	M	57	Stomach	3 yrs.	Indigestion; epigastric distress	Partial resection with posterior gastro-enterostomy	Nodular mass, the size of a dollar, in wall of stomach	Malignant lymphocytoma	Lost
G 10990	W	M	54	Stomach	3 yrs.	Indigestion; loss of weight	Exploratory laparotomy for inoperable neoplasm of stomach; autopsy specimen	Wall of stomach indurated diffusely; metastases to liver and lungs	Malignant reticuloma	Dead, metastases
G 10846	W	M	55	Stomach	9 mos.	Loss of weight; weakness; melena	Partial resection of stomach with anterior gastro-enterostomy and entero-enterostomy	Large ulcerated mass on lesser curvature; metastases to regional nodes	Malignant reticuloma	Dead, metastases
G 9671	W	M	66	Stomach	9 mos.	Anorexia; dyspnea; swelling in abdomen	No operation; autopsy specimen	Huge tumor, soft, ragged and ulcerated	Malignant reticuloma	Dead
G 7103	W	M	56	Stomach	1 yr.	Gnawing pain; eructation; vomiting; loss of weight	No operation; autopsy specimen	Hard, irregular mass, freely movable, ulcerated, involving pancreas, gallbladder, cecum and rectum	Malignant lymphocytoma	Dead, metastases
4560	W	F	..	Stomach	......	....	Pylorectomy	....	Malignant lymphocytoma	Lost

Case	Race	Sex	Age	Location	Duration	Symptoms	Small Intestine	Hard, annular tumor	Malignant reticuloma	Well *
41050	W	F	50	Ileum	1 yr.	Weakness; loss of 30 pounds (13.6 Kg.); palpable mass	Resection of terminal part of ileum; entero-colostomy	Hard, annular tumor	Malignant reticuloma	Well
41221	C	F	46	Ileum	6 mos.	Malaise; cramplike pain; diarrhea; nausea	Resection of terminal part of ileum; entero-colostomy	Annular, sacculated tumor	Malignant reticuloma	Living, 3 years, recurrence
41291	W	M	47	Ileum	......	Burning and soreness in epigastrium; "bloating"	Resection of portion of ileum; internal entero-enterostomy	Large, sacculated tumor surrounding lumen	Malignant reticuloma	Dead, recurrence
39261	W	F	36	Ileum	6 mos.	Diffuse, dragging pain in lower part of abdomen	Resection; end-to-end anastomosis	Annular tumor in distal portion	Malignant reticuloma	Unknown
35992	W	M	33	Ileum	2 mos.	Intermittent, diffuse pain in lower part of abdomen	......	Small, papillary nodule in wall of ileum	Malignant lymphocytoma	Unknown
33318(2)	W	F	19	Ileum	5 yrs.	Anemia, eructation and constipation	Excision of small nodule from duodenum	An ileocecal, annular tumor producing intussusception	Malignant reticuloma	Improved
39596	W	F	9	Ileum	2 wks.	Pain in right side	Resection of terminal part of ileum and cecum	Gangrenous, intussuscepted tumor produced by multiple, sessile tumor	Malignant lymphocytoma	Well
27187	C	M	18	Ileum	24 hrs.	Acute pain; vomiting; weakness	Resection	Firm, annular, spherical tumor	Malignant lymphocytoma	Dead, peritonitis
26103	W	M	5	Ileum	......	......	Resection of part of ileum with anastomosis	Annular tumor producing gangrenous intussusception	Malignant reticuloma	Well
21971	W	M	6 mos.	Ileum	4 wks.	Diffuse, cramplike pains; vomiting; melena	Partial resection of ileum	Hard, annular tumor producing intussusception	Malignant reticuloma	Dead, recurrence
18327	W	M	39	Ileum	7 wks.	Constipation; nausea; vomiting; cramps; blood-streaked stools; loss of weight	Resection of cecum and ileum	Multiple polypoid tumor causing intussusception	Malignant lymphocytoma	Well
16185a	C	M	24	Ileum	......	Acute intestinal obstruction	Resection of part of ileum	Tumor external to lumen, ulcerated	Malignant lymphocytoma	Dead, anemia
G 10140	W	M	77	Ileum	6 mos.	Difficulty in urination	No operation; autopsy specimen	Nodular elevation surrounding a polypoid growth	Malignant lymphocytoma	Dead, asphyxia
G 7492	W	M	12	Ileum	......	Stricture of larynx	No operation; autopsy specimen	Multiple, small sessile tumors, hard and ulcerated; metastases to brain	Malignant reticuloma	Dead, metastases
G 6346	W	M	37	Ileum	1 mo.	Nausea; vomiting; headaches; loss of vision; mental deterioration	Craniotomy for brain tumor; final; postoperative autopsy specimen	Stony hard, nodular elevation	Malignant lymphocytoma	Dead, peritonitis
G 4729	W	F	42	Duodenum	6 wks.	Pneumonia; anemia; swelling	No operation; autopsy specimen	Thickening; ulcerated plaque in ileum	Malignant lymphocytoma	Dead
G 2496	W	M	57	Ileum	1 yr.	Malaise; severe prostration after influenza	No operation; autopsy specimen	Large, hard, nodular tumor, ulceration	Malignant	Dead
G 1842	W	M	17	Ileum	3 mos.	Constipation; pain	No operation; autopsy specimen	Three tumors causing partial obstruction	Malignant lymphocytoma	Dead
G 225	W	M	27	Ileum	4 mos.	Diarrhea; vomiting; painful urination	No operation; autopsy specimen	Necrotic mass, size of a grapefruit	Malignant	Dead
UM	W	M	69	Ileum	3 wks.	Malaise; indigestion; irregular pulse	Incision and drainage; large abscess attached to ileum	......	Malignant reticuloma	Dead, peritonitis

* The term "well" signifies that the patient lived five years or longer after operation.

TABLE 2.—*Lymphoblastomas of the Gastro-Intestinal Tract (45 Cases)—Continued*

Path. No.	Race	Sex	Age	Location	Duration	Chief Symptoms	Treatment	Gross Appearance	Microscopic Type	Result
Colon										
41660	W	F	50	Cecum	10 days	Pain and constipation in right lower quadrant	Resection of ileum and cecum; lateral ileocolostomy	Sessile tumor in cecum	Malignant lymphocytoma	Dead, recurrence
32293	C	M	42	Cecum	2 mos.	Pain; bleeding; constipation	Resection of ileum and cecum; lateral anastomosis; ileocolostomy	Pedunculated mass at ileoceal valve; obstruction	Malignant reticuloma	Lost
29695	W	F	9	Cecum	3 wks.	Bleeding; pain; vomiting; mass in right quadrant	Resection of ileum and cecum; lateral anastomosis; ileocolostomy	Tumor of cecum extending over into ileum	Malignant lymphocytoma	Lost
29688	W	M	41	Sigmoid	1 yr.	Constipation; dull pain in left lower quadrant; bleeding	Exploratory laparotomy for inoperable carcinoma of sigmoid	Autopsy; large tumor, nodular, size of fist, filling pelvis	Malignant reticuloma	Dead, metastases
28312	W	F	45	Cecum	10 days	Pain and tenderness in left lower quadrant	Resection of cecum and ileum; inter anastomosis; ileocolostomy	Thickened, indurated wall of cecum	Malignant lymphocytoma	Dead, extension
22763	W	M	41	Cecum	6 wks.	Dull, burning pain; tenderness	Resection of cecum and transverse colon; lateral ileocolostomy	Two small nodules, 2 cm. in diameter in cecum	Malignant reticuloma	Lost
22475	W	M	10	Cecum	1 yr.	Pain and colic	Resection of cecum and ileum; ileal anastomosis; ileocolostomy	....	Malignant reticuloma	Lost
13564	W	F	68	Cecum	7 mos.	Nausea; vomiting; palpable mass	Resection of cecum and ileum; lateral anastomosis; ileocolostomy	Large, hollow growth of cecum; ileum adherent	Malignant reticuloma	Dead, pneumonia
12792	W	M	36	Cecum	5 mos.	Pain, right lower quadrant; lump felt 3 weeks	Resection of cecum and ileum lateral ileocolostomy	Large tumor of cecum	Malignant lymphocytoma	Well
8230	W	M	33	Cecum	3 yrs.	Diffuse gastro-intestinal upsets; pain; nausea; vomiting	Resection of cecum and portion of ileum; ileocolostomy	Large tumor of cecum; thickened, indurated walls	Malignant reticuloma	Dead, 3 months, recurrence
9035	W	F	3	Cecum	4 mos.	Colic and vomiting, intermittently	Resection of cecum and portion of ileum; lateral ileocolostomy	Cecum partly invaginated and filled by ileum growth	Malignant reticuloma	Dead, 1 month, recurrence
Rectum										
1281	W	F	75	Rectum	6 mos.	Pain in rectum and constipation	Local excision of portion of rectum with cautery	Irregular strands and large masses of tumor tissue	Malignant reticuloma	Dead, 1 year, recurrence

CONCLUSIONS

1. Forty-five cases of lymphoblastomas, formerly diagnosed as sarcomas, chronic inflammatory tumors, lymphomas or other types of growth, have been reviewed from the standpoint of their clinical and pathologic features.

2. These tumors frequently occur in young children. The site of election is the terminal part of the ileum and cecum.

3. It is difficult clinically to distinguish lymphoblastomas from carcinomas, but certain characteristics of the former have been emphasized, such as an insidious onset without acute pain, severe wasting and secondary anemia. The presence of a moderate degree of fever and the absence of early symptoms of obstruction are strongly suggestive of a tumor of lymphoid origin.

4. The characteristic gross form produced is an aneurysmal dilatation of the bowel in contradistinction to the stenosis produced by carcinoma. The typical cytologic form is that of a round cell, resembling those of the lymphoid series. The tumors are divided into two main groups, the lymphocytomas and the reticulomas, according to the cells from which they arise.

5. These tumors are thought to arise from the lymphoid tissue of the intestinal tract and represent atypical developments of the lymphocytic and reticulum cells.

6. The majority of the tumors are malignant. The remainder must be considered potentially malignant, although it is frequently impossible to distinguish the malignant characteristics. Tumors of the reticulum cell type are the more malignant. Both are frequently confused with benign inflammatory lesions such as tuberculosis and syphilis.

The prognosis is poor, owing to the late diagnosis. Optimum treatment consists of surgical resection combined with irradiation.

EROSION OF FEMORAL ARTERY, SECONDARY TO PATHOLOGIC FRACTURE DUE TO OSTEOMYELITIS

REPORT OF A CASE IN WHICH THE COMMON FEMORAL ARTERY WAS LIGATED

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The chief interest in reporting this case is the ligation of the common femoral artery because of secondary hemorrhage incident to the erosion of the vessel. The second feature is the presence of two pathologic fractures, one of the surgical neck of the humerus, and the other in the shaft of the femur, the latter being directly responsible for the erosion of the superficial femoral artery.

Pathologic fracture in osteomyelitis can be prevented in practically all cases treated by the Orr method primarily. Over two hundred patients have been treated by the Orr method in this clinic since 1923, with only one case of secondary pathologic fracture. This occurred in a femur which went unprotected by the usual plaster hip spica for only one day. This same patient, who had multiple lesions, completely recovered.

The possibility of secondary hemorrhage, especially of mechanical trauma incident to pathologic fracture, makes Orr's dictum of adequate rest and protection following the primary adequate drainage absolutely essential in the treatment of osteomyelitis. This principle, in our opinion, cannot be ignored, regardless of the method used in the treatment of pyogenic involvement of bone.

Ligation of the common femoral artery is not a frequent procedure, except as a life-saving measure, preliminary to amputation. The collateral circulation of this part of the femoral vessel is certainly more efficient than is usually considered to be the case. In this patient amputation was performed no less than twenty-eight days after the ligation. This was necessary because of the septic absorption from the extensively involved femur.

REPORT OF A CASE

In Avis C., aged 13, white, the onset of the present illness was typically acute, following a moderate trauma to the right knee. After a stormy period of seven weeks, the right thigh was finally but inadequately drained by two soft tissue stab wounds. One week before her admission to the hospital she moved her right leg, and experienced severe pain and a sense of breaking in the right thigh.
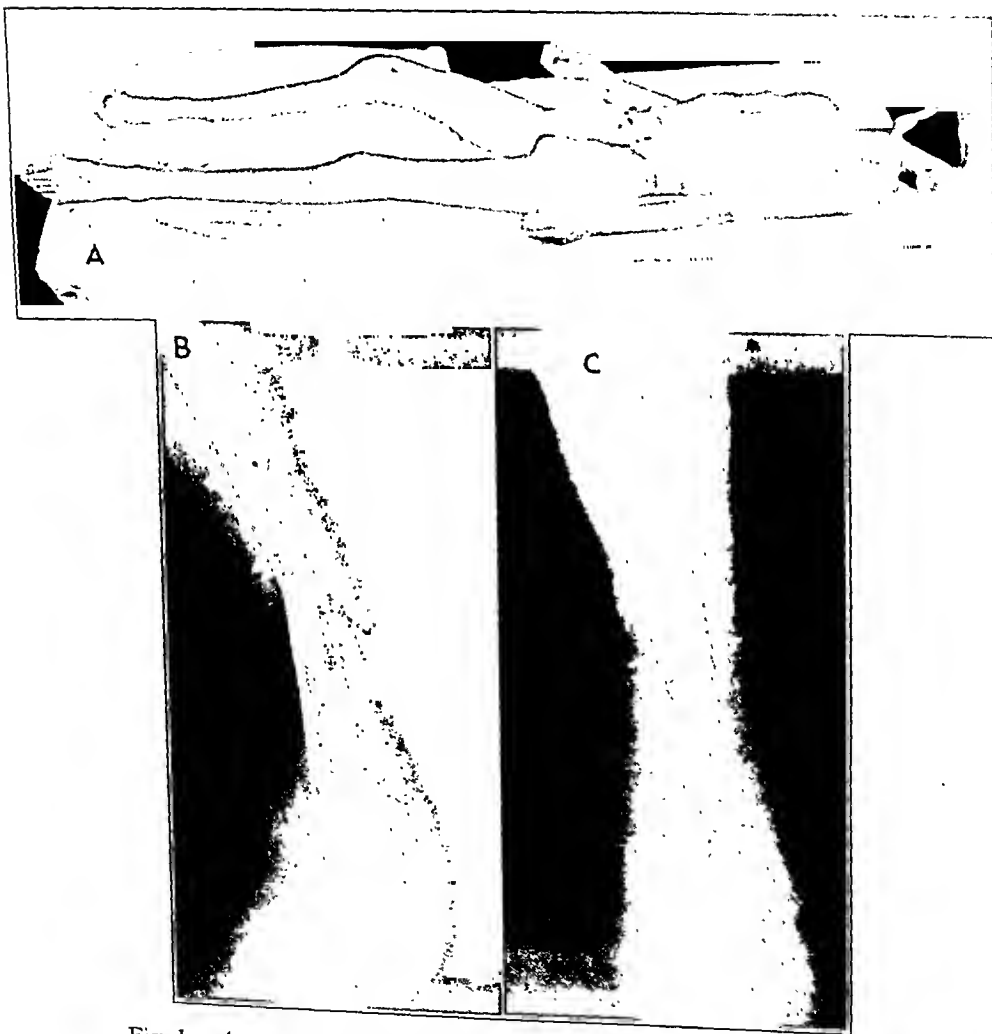
Fig. 1.—*A*, the patient on her admission to the hospital, Jan. 20, 1932; *B* and *C*, the lateral and anteroposterior roentgenograms of the right femur. The lower two thirds of the shaft is involved. There is remarkably little displacement at the pathologic fracture site.

On admission to the hospital on Jan. 20, 1932, she was in great pain, and was markedly emaciated. On examination, the right thigh was enlarged, tender, bowed anterolaterally, and crepitated on gentle manipulation. The right shoulder was tender and fluctuating, and grated.

The temperature ranged from 101 to 104 F., the pulse from 110 to 150, and the respirations around 40. The leukocyte count was 13,400, the hemoglobin 80 per cent and the red cell count 3,620,000. The urine was normal, and the Wassermann tests negative, but the intradermal tuberculin tests, both human and bovine, were positive on several occasions. The blood cultures were negative. The coagulation period was three minutes.

The child was extremely septic on admission, the period of her illness now being of thirteen weeks' duration. The active pulmonary findings were suggestive of tuberculosis. All these factors made the operative risk too great. A hip spica
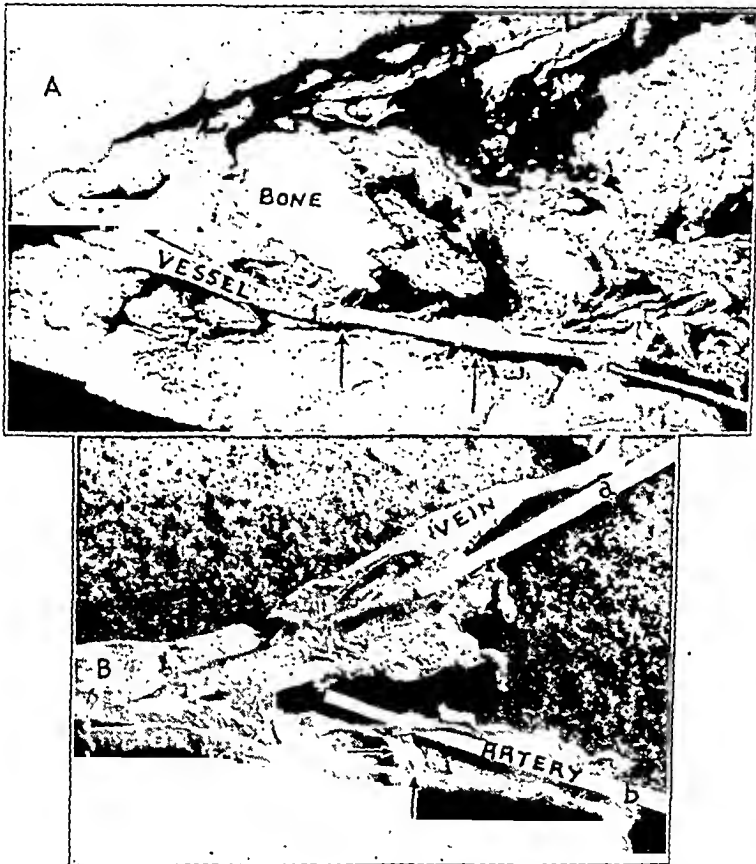
Fig. 2.—*A*, postamputation dissection of the right thigh and femur. The arrows indicate the contact points of the vessels with the jagged distal fragment. *B*, the superficial femoral artery and vein dissected free and opened. The venous defect (*a*) could not definitely be attributed to erosion. The artery with the indicator passing through the erosion is shown by *b*. In the lumen, contiguous to the opening but not entirely blocking it, is observed an organized thrombus.

was applied under anesthesia, and further hygienic measures instituted to improve the patient's resistance.

On February 10, Orr drainage was done on the right femur through a window in the cast. Free pus was not encountered except in Scarpa's triangle. The bone in the region of the fracture was necrotic, exhibiting a somewhat yellowish, caseous appearance, suggesting tuberculosis. Guinea-pig inoculation and microscopic

examination of tissue gave negative results. The bacteriologic examination proved Staphylococcus albus to be the etiologic agent. The recovery was uneventful.

On March 16, the sequestrated upper half of the right humerus was gently removed from a sinus located over the upper lateral aspect of the shoulder, without anesthesia.

The first massive hemorrhage suddenly occurred about one month after the operation on the femur. The patient rapidly exhibited symptoms of shock and finally syncope. Examination of the wound failed to reveal any actively bleeding
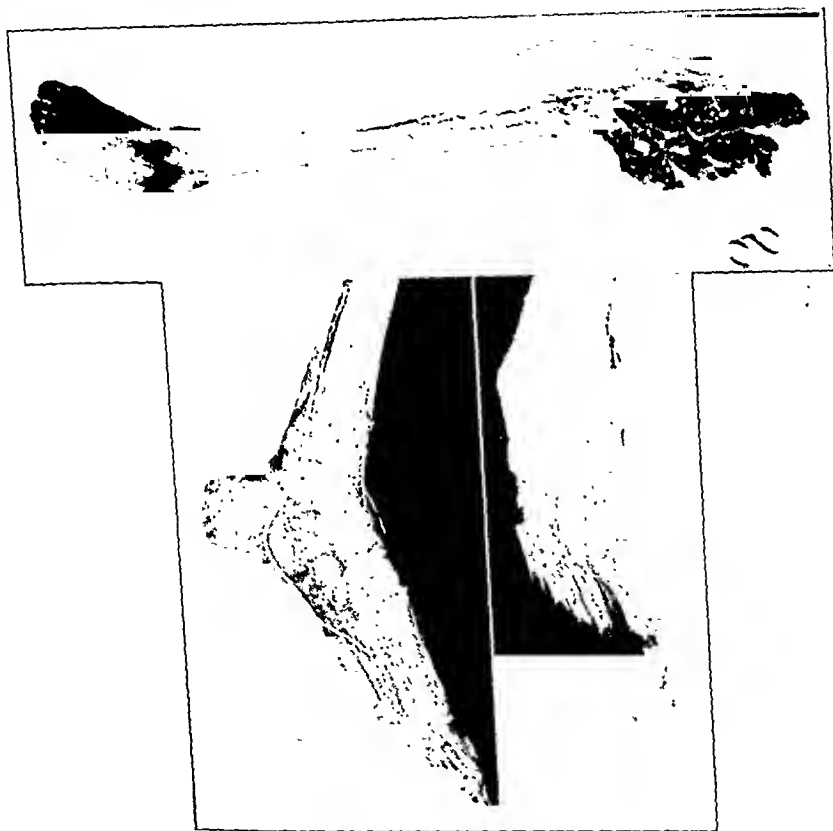
Fig. 3.—The amputated right lower extremity twenty-eight days after ligation of the common femoral artery. Except for the discoloration of the heel, the parts are in excellent condition. The terminal vessels are impermeable to the opaque solution injected immediately after amputation.

points. Transfusion of citrated blood and dextrose administered intravenously revived her. In the next two days she had two more extensive hemorrhages, from which she recovered following the same treatment.

Immediately after the third hemorrhage, the right common femoral artery was ligated directly below Poupart's ligament, under local anesthesia in the ward.

On regaining consciousness, the patient complained of numbness of the entire extremity, and pain over the dorsum of the foot and heel. The foot remained cold and colorless for the remainder of that day. On the second day the foot became

warm, but was still somewhat painful. The extremity, below the knee, exhibited almost complete anesthesia during the entire period of observation until amputation. There was no level of hyperesthesia noted at any time. Of particular interest was the observation that no ischemic contractures occurred. Following ligation, the red cell count steadily rose from less than 2,000,000 to about 4,000,000 at the time of discharge from the hospital. No further hemorrhages ensued.

Septic absorption necessitated further drastic measures, and twenty-eight days after ligation, a Guillotine amputation of the right thigh was done at the junction
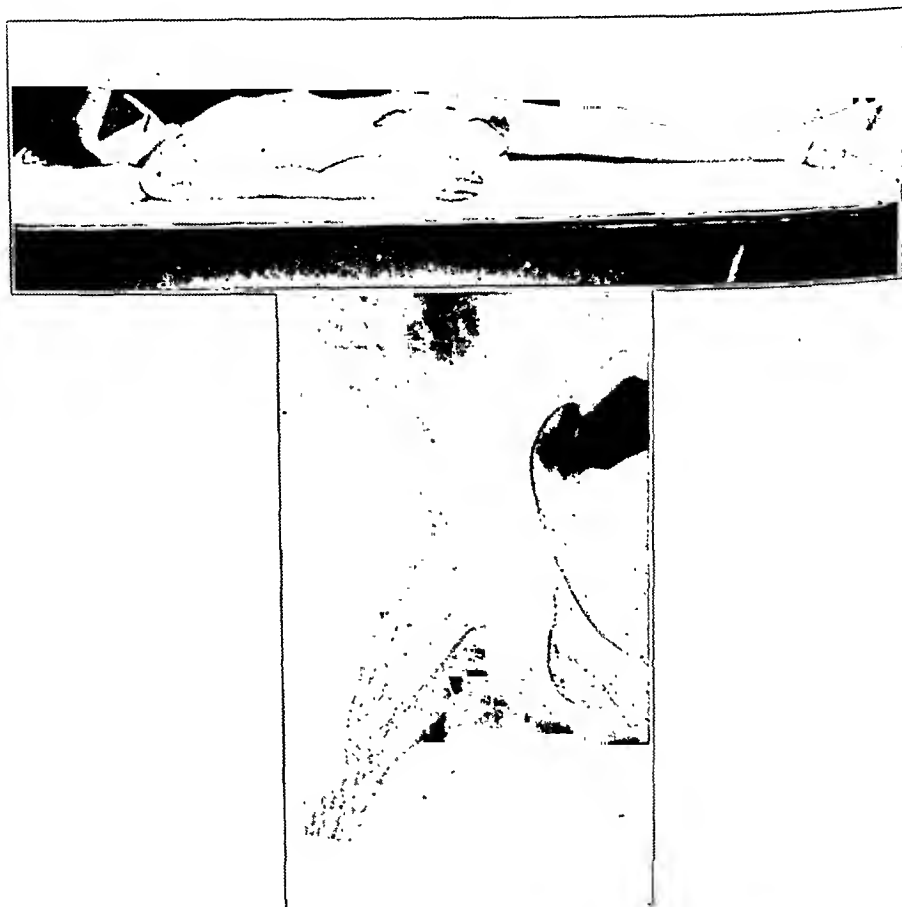
Fig. 4.—The patient two months after amputation, and the roentgenogram of the stump of the same period.

of the upper and middle thirds of the thigh, which was just above the site of the pathologic fracture.

The amputated extremity was immediately dissected, and the superficial femoral artery was found to be eroded opposite the jagged distal fragment, at which point the vessel was in contact with the bone. The accompanying vein also presented a defect which could not be absolutely ascertained as being due to erosion. On opening the femoral artery, an organized thrombus was found contiguous to the erosion, but not completely blocking it. The muscles of the leg were pale, but otherwise not remarkable. Histologic examination of the vessel wall, thrombus and a section of the gastrocnemius muscle revealed: erosion of the femoral artery, organizing

thrombus and ischemia of the muscle. The superficial femoral artery was then injected at its uppermost limit with an opaque solution, and roentgen examination was made. All the vessels filled readily except the terminal phalangeal branches. Further dissection corroborated these roentgen findings.

The patient made an uneventful recovery, and was discharged about two months after the last operative procedure. The stump was almost completely healed.

COMMENT

Several questions readily present themselves regarding the treatment in such a case. It may be stated at the outset that this extreme degree of involvement will not likely occur if adequate primary drainage is established as soon as the diagnosis of osteomyelitis is made.

1. Should primary amputation be considered at the first examination of a patient presenting this picture?

Fig. 5.—*A*, roentgenogram of the right shoulder on the patient's admission, showing the pathologic fracture of the surgical neck of the humerus. The upper one half of the shaft is sequestrated. *B*, the same shoulder three months after sequestrectomy. The head of the humerus is apparently viable and is united to the distal fragment. The functional result is good.

Many limbs have been spared in this clinic by following the regimen as instituted in the case reported. A primary adequate cast, in the great majority of cases, will enable the patient to develop sufficient resistance to combat the infection, after final drainage has been established. Amputation is resorted to only as a life-saving measure. Cases are on record in this clinic that wholly substantiate this procedure.

2. What is the danger of secondary hemorrhage following an extensive drainage of the femur?

It is minimum if the operator confines himself to the lateral side of the thigh, and limits his manipulations to blunt dissection in the region of the great vessels.

3. Can one cope successfully with a secondary hemorrhage when a cast has been applied?

The window in the cast can readily be removed if necessary, and the operative field quickly exposed. The cast will certainly minimize the patient's early excitable movements and tend to lessen the degree of hemorrhage.

4. Is it safe to operate through a window in the cast, as advocated by Orr?

The window should be adequate to permit easy access to all parts of the field of operation. This method saves so much time in poor risks, that the possible disadvantages are outweighed by the benefits to the patient.

CONCLUSION

A case has been reported of ligation of the common femoral artery secondary to erosion of the vessel incident to a pathologic fracture in osteomyelitis. To the list of complications of osteomyelitis is added and elaborated erosion of the femoral artery, which has been but seldom reported in the literature. Special emphasis has been placed on the prevention of pathologic fracture in osteomyelitis by adequate protection as advocated by Orr.

BLOOD SUPPLY OF THE LARGE INTESTINE

ITS SURGICAL CONSIDERATIONS

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HISTORICAL

The historical background for the blood supply of the colon does not extend beyond Galen[1] (131-201 A.D.), as he was the first to describe arteries as carriers of blood. However great Galen's services may have been to medicine in his day, his influence in the long run was retrogressive. Philosophy was an integral part of the learning of every scholar of his time, and philosophic beliefs and concepts were inextricably mingled with scientific facts. Galen might have discovered many more anatomic and physiologic facts had he not hidden science behind a screen of theory regarding the spirits of the body. Bodily functions were ascribed to the agency of these spirits, and research was abandoned when the spirits entered. One result of this philosophic belief is evidenced in Galen's anatomic diagrams,[2] which show vessels coursing vaguely from intestine to liver, but nothing definite and clearcut.

In the following centuries and in the Middle Ages, Christianity replaced philosophy as a stumbling block to advance in the knowledge of anatomy.[3] Owing to ascetic doctrine, the body was regarded as the temporary and unworthy abode of the soul during life, and in illness treatment of the soul was almost always incorporated with, if not substituted for, measures to relieve the body. However, with death came a change in attitude toward the body, which was looked on now as a sacred relic with which the soul would some day reunite. These two

1. Buck, A. H.: The Growth of Medicine, New Haven, Conn., Yale University Press, 1917, p. 169; Cyclopaedia of Anatomy and Physiology, London, Longman, Brown, Green, Longmans & Roberts, 1835-1836, vol. 1, p. 220. Garrison, F. H.: An Introduction to the History of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1929.

2. Singer, C. J.: The fasciculo di medicina, Florence, R. Lier & Co., 1925, plate 63.

3. Singer, C J.: The Evolution of Anatomy, New York, Alfred A. Knopf, 1925.

strangely antipathetic ideas were powerful factors in keeping exact knowledge of what was within the body at a minimum and in preventing discovery of the details of anatomy. An illustration in a late thirteenth century provincial manuscript [4] shows loops of intestine with indefinite vessels. The arterial diagrams of Vesalius [5] about 1538 indicate the inferior mesenteric artery but confuse the superior mesenteric artery and the celiac axis. More than a century later (1653), Culpepper [6] shows the same confusion in his translation of Veslingius' work. It is paradoxical that the anastomosis of the mesenteric arteries should be named for Jean Riolan, as Riolan,[7] to whom Harvey [8] refers as "prince of anatomists," is famous for his opposition to Harvey's principle of the circulation of the blood.

After the acceptance of the idea of the circulation of the blood, von Haller,[9] writing between 1759 and 1766, gave a thorough and comprehensive description of the blood supply of the colon. The emphasis he placed on the blood supplied by anastomosis from the hypogastric, spermatic, intercostal, capsular and lumbar arteries probably started some of the misconceptions regarding them. However, von Haller established the fact that the primary blood supply of the colon is from branches of the superior and inferior mesenteric arteries, and that the adjacent branches anastomose near the wall of the colon. With the exception of variations of individual branches (which will be considered separately) and detail of description, the following anatomists agree with the fundamental outline of von Haller: Cheselden,[10] Cruveilhier,[11] von Behr,[12] Wilson,[13] Smith,[14] Henle,[15] Hyrtl,[16] Quain,[17] Treves,[18]

4. Chouland, J. L.: History and Bibliography of Anatomic Illustrations, Chicago, University of Chicago Press, 1920, p. 55.

5. Vesalius, Andreas: Des Andreas Vesalius sechs anatomische Tafeln vom Jahre 1538, in Lichtdruck neu herausgegeben und der 86 Versammlung Deutscher Naturforscher und Arzte zur Feier der 400 Wiederkehr des Jahres seiner Geburt dargeboten von Moriz Holl und Karl Sudhoff, Leipzig, J. A. Barth, 1920.

6. Veslingius, Joannes: The Anatomy of the Body of Man, translated by Nicholas Culpepper, London, P. Cole, 1653.

7. Riolan, Jean, quoted by Eycleshymer, A. C.: Anatomical Names, New York, William Wood & Company, 1917, p. 321.

8. Harvey, William: De motu cordis, London, Nonesuch Press, 1928, p. 121.

9. von Haller, Albert: First Lines of Physiology, Troy, Obadiah Penniman & Co., 1803, p. 368.

10. Cheselden, William: The Anatomy of the Human Body, ed. 13, London, 1792, p. 188.

11. Cruveilhier, Jean: Anatomy of the Human Body, New York, Harper & Bros., 1844, p. 509.

12. von Behr, Alfred: Handbook of Human Anatomy, Philadelphia, Lindsay & Blakiston, 1847, p. 323.

13. Wilson, Erasmus: A System of Human Anatomy, Philadelphia, Blanchard & Lea, 1858, p. 323.

Sobotta,[19] Sappey,[20] Spalteholz,[21] Gray,[22] Cunningham,[23] Morris,[24] Merkel,[25] Toldt,[26] Gerrish,[27] Hartmann,[28] and Piersol.[29] None of the writers disagreed with the conception generally accepted of the blood supply of the colon.

THE COLON

The study of the blood supply of the colon, from the ileocecal valve to the iliac colon or sigmoid, was made with tissue removed at necropsy. More than eighty specimens were removed and examined, but only forty, in which the blood supply of the entire part could be determined exactly, and casts or roentgenograms preserved, are used in this report. Two slightly different methods were followed in this study. The first method consisted of removal, inspection, injection of celluloid solution into the arteries and corrosion of the tissue; the second method consisted of injection of the arteries in situ with a solution of red lead, removal of the specimen, roentgenologic examination and inspection of the specimen. The study of the arteries of the wall of the colon was made by: (1) inspection of the celluloid casts, (2) stereoscopic roentgeno-grams and flat roentgenograms of the wall of the colon, (3) serial

14. Smith, H. H.: Anatomical Atlas, Philadelphia, Blanchard & Lea, 1859, p. 148.

15. Henle, F. G. J.: Handbuch der systematischen Anatomie des Menschen: Gefässlehre, Braunschweig, F. Vieweg und Sohn, 1871, vol. 3, pt. 1, pp. 161 and 295.

16. Hyrtl, Joseph: Handbuch der topographischen Anatomie, Vienna, W. Braumüller, 1871.

17. Quain, Jones: Elements of Anatomy, London, Longmans, Green & Co., 1914, vol. 2, pt. 2, p. 129.

18. Treves, Frederick: The Anatomy of the Intestinal Canal and Peritoneum in Man, London, H. K. Lewis, 1885.

19. Sobotta, Johannes: Atlas and Text-Book of Human Anatomy, Philadelphia, W. B. Saunders Company, 1907, vol. 3, p. 57.

20. Sappey, quoted by Potherat, Bull. Soc. anat. de Paris 3:233 (March) 1889.

21. Spalteholz, Werner: Hand-Atlas of Human Anatomy, Philadelphia, J. B. Lippincott Company, 1922, vol. 2, p. 442.

22. Gray, Henry: Anatomy of the Human Body, Philadelphia, Lea & Febiger, 1924, p. 930.

23. Cunningham, D. J.: Text-Book of Anatomy, ed. 5, New York, William Wood & Company, 1921, pp. 41-79; 930-933; 1162; 1220-1222 and 1249-1256.

24. Morris, Henry: Human Anatomy, ed. 7, Philadelphia, P. Blakiston's Son & Co., 1923, pp. 633 and 1204.

25. Merkel, Friedrich: Die Anatomie des Menschen, Wiesbaden, J. F. Bergmann, 1918, vol. 6, p. 143.

26. Toldt, Karl: An Atlas of Human Anatomy, New York, Rebman Co., 1919.

27. Gerrish, F. H.: A Textbook of Anatomy by American Authors, Philadelphia, Lea Bros. & Co., 1899, p. 429.

28. Hartmann, Henri: Some Considerations upon High Amputation of the Rectum, Ann. Surg. 50:1091 (Dec.) 1909.

29. Piersol, G. A.: Human Anatomy, Philadelphia, J. B. Lippincott Company, 1919, pp. 802 and 1672.

section of the wall of the colon and microscopic examination and (4) dissection of the wall of the colon under lower power magnification.

First Method.—The removal was planned to include all of the arteries supplying the colon from their origins. The small bowel was removed from within 12.5 cm. of the ileocecal valve to the duodeno-jejunal flexure, the omentum was cut close to the greater curvature of the stomach and reflected downward, the peritoneum was incised lateral to the ascending and descending colon, across the brim of the true pelvis and along the upper border of the pancreas, and the colic ligaments were cut close to their mural attachments. Along the lateral incisions, the colon, the peritoneum, the colic vessels and the subperitoneal fat were reflected toward the median line. At the duodeno-jejunal flexure the peritoneum was incised close to the bowel and reflected mesially from the anterior surface of the duodenum. The mesocolon was reflected downward from the anterior surface of the pancreas and duodenum. The superior mesenteric artery was severed immediately distal to the origin of the inferior pancreaticoduodenal artery, the entire mass reflected downward, the inferior mesenteric artery cut at its origin and the reflection continued to the pelvic brim where the sigmoid and sigmoid arteries were cut across. The entire mass was removed from the abdominal cavity.

The specimen, consisting of the omentum, the entire colon with its peritoneal attachments and arteries, was subjected to careful examination and the measurements of each specimen were recorded on a printed form. The length and size of the different parts of the colon and the origin and course of the main arteries and marginal artery were recorded.

Thirty-five unembalmed specimens were used for injection of celluloid solution into the arteries and subsequent corrosion of the tissue. The process, with a few modifications, was similar to that used in studies of the blood supply of other organs by Barker,[30] Whitten,[31] Pope and Judd,[32] and Counseller and McIndoe.[33] The lumen of the colon as well as the arteries was injected in eighteen specimens.

The advantage of this method is that an accurate cast of the complete arterial supply of the specimen is preserved and the results of the

30. Barker, N. W.: Celluloid Corrosion Technic for Study of Normal and Pathologic Variations of the Arteries of the Kidney, J. Lab. & Clin. Med. **14**:257 (Dec.) 1928.

31. Whitten, M. B.: A Review of the Technical Methods of Demonstrating the Circulation of the Heart; a Modification of the Celluloid and Corrosion Technic, Arch. Int. Med. **42**:846 (Dec.) 1928.

32. Pope, C. E., and Judd, E. S.: The Arterial Blood Supply of Sigmoid, Rectosigmoid and Rectum, S. Clin. North America **9**:957 (Aug.) 1929.

33. Counseller, V. S., and McIndoe, A. H.: Dilatation of the Bile Ducts (Hydrohepatosis), Surg., Gynec. & Obst. **43**:729 (Dec.) 1926.

inspection are checked. The disadvantage lies in the technical difficulties of removal, injection and subsequent handling of the bulky, fragile specimens.

Second Method.—The arteries of fifteen specimens were injected in situ with opaque material; the specimens were then removed, roentgenograms were taken, specimens were inspected and the results recorded. The inferior mesenteric artery was clamped at its origin from the aorta and the sigmoid arteries, and the marginal artery of the sigmoid was clamped at the brim of the pelvis. The superior mesenteric artery was isolated and severed just distal to the origin of the inferior pancreaticoduodenal artery. A syringe was tied into the distal end of the artery and the vessel was washed with water until the blood disappeared from the fine vessels of the intestine. A warm, hemogenous mixture of about three parts corn starch, two parts red lead and four parts warm water was injected with a syringe. When the small vessels of the intestine were filled, the injection was stopped and the specimen was undisturbed for several hours so that the starch might harden.

The specimen was removed in a manner similar to that described in the first method. It was then spread to its full extent on an aluminum tray with a film immediately beneath, the lumen of the bowel was filled with water, and plates were made for stereoscopic study. The specimen was inspected as in the first method, the results being checked by the roentgenograms. The advantage of this method over the first is that it presents far less technical difficulty.

Embryology.—A brief review of the embryologic development of the colon will give a clearer idea of the condition found in the adult and enables better evaluation of reported anomalies of the blood supply.

Arey,[34] Bailey and Miller,[35] Broman,[36] Dott,[37] Cunningham,[23] Huntington,[38] Jordan,[39] McMurrich,[40] Mall,[41] Morris,[24] Frazer and

34. Arey, L. B.: Developmental Anatomy: A Text-Book and Laboratory Manual of Embryology, Philadelphia, W. B. Saunders Company, 1924.

35. Bailey, F. R.: Textbook of Histology, ed. 7, New York, William Wood and Company, 1927. Bailey, F. R., and Miller, A. M.: Text-book of Embryology, ed. 4, New York, William Wood and Company, 1923.

36. Broman, Ivar: Normale und abnorme Entwicklung der Menschen, Wiesbaden, J. F. Bergmann, 1911.

37. Dott, N. M.: Anomalies of Intestinal Rotation: Their Embryology and Surgical Aspects with Report of Five Cases, Brit. J. Surg. **11**:251 (Oct.) 1923.

38. Huntington, G. S.: The Anatomy of the Human Peritoneum and Abdominal Cavity, Philadelphia, Lea Bros. & Co., 1903.

39. Jordan, H. E.: A Text-Book of Histology, New York, D. Appleton and Company, 1924.

40. McMurrich, J. P.: The Development of the Human Body, ed. 7, Philadelphia, P. Blakiston's Son & Co., 1923, p. 307.

41. Mall, F. P.: Development of the Human Intestine and Its Position in the Adult, Bull. Johns Hopkins Hosp. **9**:197 (Sept.-Oct.) 1898.

Robbins,[42] Pernkopf,[43] Hertzler,[44] Prentiss and Arey,[45] and Piersol [29] are in agreement regarding the principal changes that take place in the embryologic development of the intestinal tract.

In the stage of the primitive streak, an infolding of the entoderm and the splanchnic layer of mesoderm begins. The edges of these two infolding sheets of tissue meet and fuse, forming a tube in the longitudinal axis of the embryo. This early intestine is attached through its entire length to the posterior wall of the embryo by the dorsal mesogastrium and is connected ventrally at its midpoint to the yolk sac. At this stage it is customary to distinguish three parts of the intestinal tract: (1) the foregut, which has a ventral as well as a dorsal mesentery; (2) the midgut, from which develop the lower part of the duodenum, the remainder of small intestine and the ascending and transverse colon, and (3) the hindgut, from which the remainder of the intestinal tract develops. For this study, only the midgut and hindgut need be considered.

The midgut increases in length, producing an anterior bend and a lengthened dorsal mesentery. The first part of the hindgut grows cephalad and, if not pulled upward, is anchored by a retention band of mesenchymal tissue which is described by Frazer and Robbins and by Dott, extending from the root of the superior mesenteric artery to the region of the splenic flexure. The upper part of the hindgut is then nearer the cephalic end of the embryo than is the first part of the midgut. The latter is depressed by the umbilical vein which is pulled downward across it by the enlarging liver. With the first part of the midgut depressed and the distal end anchored, rapid growth takes place. Due either to lack of intra-abdominal space or to a pull from the diminishing yolk stalk, the midgut is extruded into the coelomic cavity through the large umbilical opening. This extrusion is referred to as the embryologic or physiologic umbilical hernia (fig. 1), and is first seen between the 4 and the 10 mm. stage of the embryo. The midgut in the umbilical hernia lies outside the abdominal cavity proper and has no contact with other developing viscera. At approximately the 40 mm. stage of the embryo the intestines return to the abdominal cavity because of the pull exerted by the descending liver on the loops near the dorsal attachment, or because the change in pressure resulting from intra-abdominal enlargement sucks them back. After reentering the abdomen the intestines assume the general position seen at birth.

42. Frazer, J. E., and Robbins, R. H.: On the Factors Concerned in Causing Rotation of the Intestine in Man. J. Anat. **50:**75 (Oct.) 1915.

43. Pernkopf, Eduard: Die Entwicklung der Form des Magen-Darm-Kanales beim Menschen. Ztschr. f. d. ges. Anat. **85:**1, 1928.

44. Hertzler, A. E.: The Peritoneum, St. Louis, C. V. Mosby Company, 1919.

45. Prentiss, C. W., and Arey, L. B.: A Laboratory Manual and Text-Book of Embryology, ed. 3. Philadelphia, W. B. Saunders Company, 1922.

During the existence of the umbilical hernia notable development in the blood vessels which supply the bowel takes place. Huntington stated that the main branches of the superior mesenteric artery are present during this stage. Pernkopf, in a detailed study, reported that the first identifiable branch of the superior mesenteric artery is the ileocolic in an embryo of 16.7 mm.; in an 18 mm. embryo the middle and left colic arteries are present, and in a 33.5 mm. embryo the vessels are present and are used to identify the parts of the colon.

The great omentum is in intimate relationship with the colon and its development deserves consideration. The embryologic development of the omentum as described by Arey, Hertzler, Huntington, Cunning-
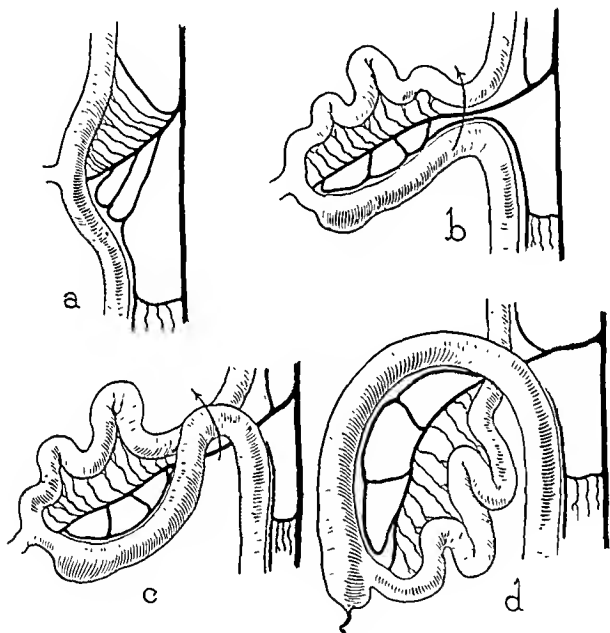
Fig. 1.—Embryologic hernia and rotation of the midgut.

ham, Piersol and Lockwood [46] is constant. The omentum develops from the dorsal mesentery of the stomach as that organ undergoes rotation to the left, descends and assumes a somewhat horizontal position between the 5 to 17 mm. stages of the embryo. The omentum forms a double layered, anterior wall for the lesser peritoneal cavity, and as it grows downward, it lies on the intestines as a flat bag with one lip attached to the greater curvature of the stomach and the other to the posterior abdominal wall.

46. Lockwood, C. B.: The Development of the Great Omentum and Transverse Mesocolon, J. Anat. & Physiol. **18**:257, 1883-1884; On the Development of the Arteries of the Abdomen and Their Relation to the Peritoneum, Proc. Roy. Soc. London **38**:485, 1884-1885.

Main Arteries: In the "Basle Anatomical Nomenclature"[53] the arteries to the colon derived from the superior mesenteric artery are: ileocolic, right colic and middle colic, and from the inferior mesenteric, the left colic. Each of these arteries will be described separately.

The ileocolic artery is generally described as the last artery given off on the right side of the superior mesenteric artery and as one of its two terminal branches. The terminal branches of the ileocolic artery are designated: (1) a colic branch which ascends along the wall of the colon; (2) an ileac branch which continues downward and then to the left along the terminal portion of the ileum to anastomose with the last intestinal artery and enclose the avascular area of Treves; (3) an anterior cecal artery which courses downward to the anterior surface of the cecum; (4) a posterior cecal artery which passes to the posterior surface of the cecum, and (5) the artery to the appendix. In the extensive work of Kelley,[54] Deaver,[55] and Jonescu and Juvara,[56] on the arteries of this region, not only are five main branches of the ileocolic artery described, but the irregularity of the origin of these vessels is emphasized.

In every specimen of this study the ileocolic artery coursed to the right toward the ileocecal valve. The general course of the artery varied slightly with the position of the ileocecal valve, which in turn is dependent on the descent of the cecum before and after birth. The artery subdivides at a distance from the ileocecal valve varying from 2.5 to 9 cm., but in the majority of specimens the distance is about 6 cm. As a rule, the first branch to be given off by the ileocolic artery is the ascending colic (figs. 2 and 3), but one of the cecal branches may arise first (figs. 4 and 5). In some cases there are several ascending colic branches (figs. 6 and 7). In specimens in which the ileocolic artery divided at a considerable distance from the ileocecal valve, anastomosis between the branches sometimes occurred (fig. 4).

The artery to the appendix, although usually originating from the posterior cecal branch of the ileocolic artery, may be given off by one of the other branches, or may have an independent origin directly from the ileocolic artery. In one specimen the appendix is supplied by seven distinct branches from the posterior cecal and ileal arteries.

53. Emmel, V. E.: The B N A Regional and Systematic Anatomy, Philadelphia, Wistar Institute Press, 1927.

54. Kelley, H. A.: The Vermiform Appendix and Its Diseases, Philadelphia, W. B. Saunders Company, 1905.

55. Deaver, J. B.: Appendicitis, ed. 4, Philadelphia, P. Blakiston's Son & Co., 1913, p. 56; Surgical Anatomy of the Human Body, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1927, vol. 3, p. 426.

56. Jonescu, Toma, and Juvara, Ernest: Anatomie des ligaments de l'appendice vermiculaire et de la fosette iléo-appendiculaire. Progrès méd. **19**:273; 303; 321; 353; 369, 1894.

In regard to the ileocolic artery, it may be concluded: (1) the existence of the artery is constant; (2) its course is toward the ileocecal valve and varies slightly with the position of the valve, and (3) the terminal branches of the artery vary in their origin.

The right colic artery is described as the second artery from the right side of the superior mesenteric artery. Its course is to the right, below the mesocolon to the region of the hepatic flexure of the colon. The right colic artery is the most inconstant of the colic arteries. Early

Fig. 2.—Posterior view of a specimen injected with opaque material showing: (1) the ascending colic artery as the first branch of the ileocolic artery; (2) the artery to the appendix from the ileocolic artery; (3) the absence of the right colic artery, and (4) failure of the marginal artery and anastomosis between the ileocolic and middle colic arteries.

anatomists, such as von Haller, failed to describe the right colic artery, and later Hyrtl and Henle refer to its presence by saying that two or three arteries to the colon come from the superior mesenteric artery. All modern anatomists and writers on surgical subjects describe the artery but call attention to a variable origin, either from the ileocolic or middle colic arteries. The absence of the right colic artery is given

an evolutionary background by Waldeyer,[57] who stated that in primates it was seen only once and then as a feeble branch in a gorilla. Waldeyer stated his belief that the artery should be named only when it has an independent origin from the superior mesenteric artery, and he found the independent origin to occur in about 50 per cent of cases. This view is evidently held by Fetterolf, who reported the absence of the artery in several cases. Hartmann [58] found this artery with an independent
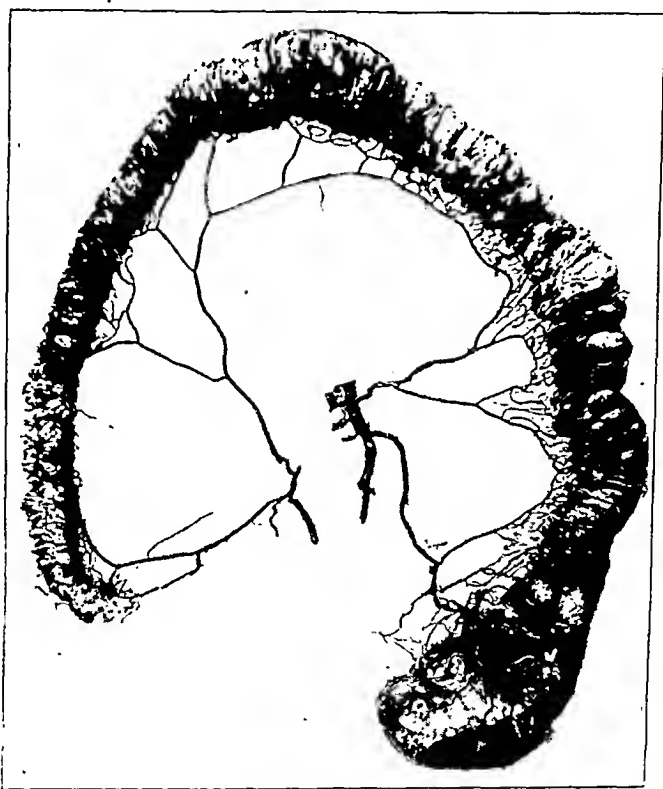
Fig. 3.—Posterior view of celluloid cast of a specimen showing: (1) the ascending colic artery as the first branch of the ileocolic artery; (2) the origin of the right colic artery from the middle colic artery, and (3) the large ascending branch of the left colic artery with several branches to the marginal artery.

origin only once in fifteen subjects, and Lardennois and Okinczyc [59] described the disposition of three colic arteries from the superior

57. Waldeyer, H. W. G.: Die Kolon-Nischen, die Arteriae colicae und die Arterienfelder der Bauchhöhle, nebst Bermerkungen zur Topographie des Duodenum und Pankreas, Berlin, G. Reimer, 1900.

58. Hartmann, Henri: Traveaux de chirurgie anatomo-clinique, S. 3 Chirurgie de l'intestin, p. 125, Paris, G. Steinheil, 1907.

59. Lardennois, G., and Okinczyc, J.: La véritable terminaison de l'artère mésentérique supérieure. Deductions pathologiques, Bull. Soc. anat. de Paris **12:**13 (Jan.) 1910.

mesenteric artery as exceptional. Jamieson and Dobson,[60] in a series of more than thirty cases, found the right colic artery as a direct branch from the superior mesenteric artery in less than 50 per cent, as a branch of the ileocolic artery in about 30 per cent and as a branch of the middle colic artery in some others.

A consideration of the existence of the right colic artery becomes academic when a particular origin is insisted on before naming the artery. If there is a vessel from the superior mesenteric, middle colic
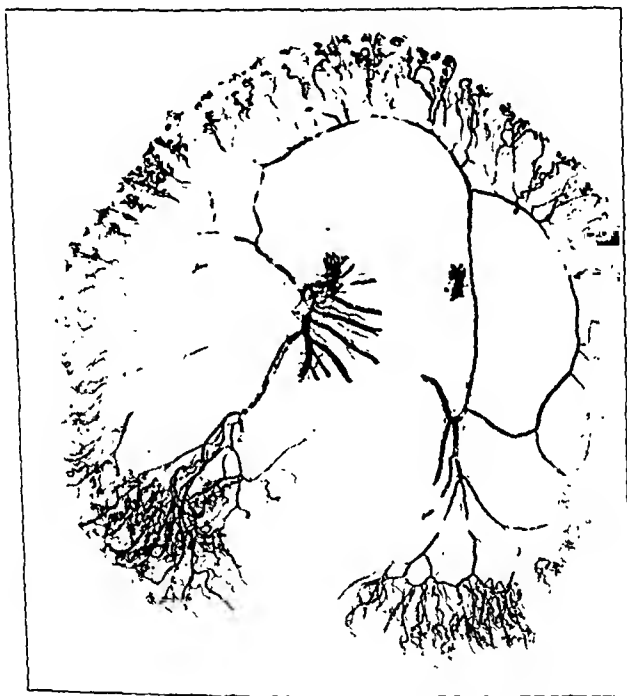
Fig. 4.—Specimen injected with opaque material showing: (1) the anterior cecal artery as the first branch of the ileocolic artery; (2) anastomosis between the branches of the ileocolic artery; (3) the origin of the right colic artery from the ileocolic artery, and (4) slight anastomosis between the ileocolic and right colic arteries.

or ileocolic artery that approximates the course of the right colic artery, which supplies the colon in the region of the hepatic flexure and anastomoses with the adjacent colic arteries, a right colic artery may be said to exist.

In the specimens studied the variations of the right colic artery were marked. The artery originated from the superior mesenteric in 40 per cent of the cases (figs. 4 and 7), from the middle colic in 30 per

60. Jamieson, J. K., and Dobson, J. F.: The Lymphatics of the Colon, Ann. Surg. **50**:1077 (Dec.) 1909.

cent of the cases (fig. 3), from the ileocolic in 12 per cent (fig. 6), whereas in 18 per cent there was no artery that corresponded in course or distribution to the right colic artery (fig. 2). Sometimes the right colic artery was small, and in these cases the deficiency was compensated for by large middle colic and ileocolic vessels. It may be concluded that the right colic artery is extremely variable in presence, origin and size.

The middle colic artery is described as the first artery coming from the right side of the superior mesenteric artery. It runs to the right
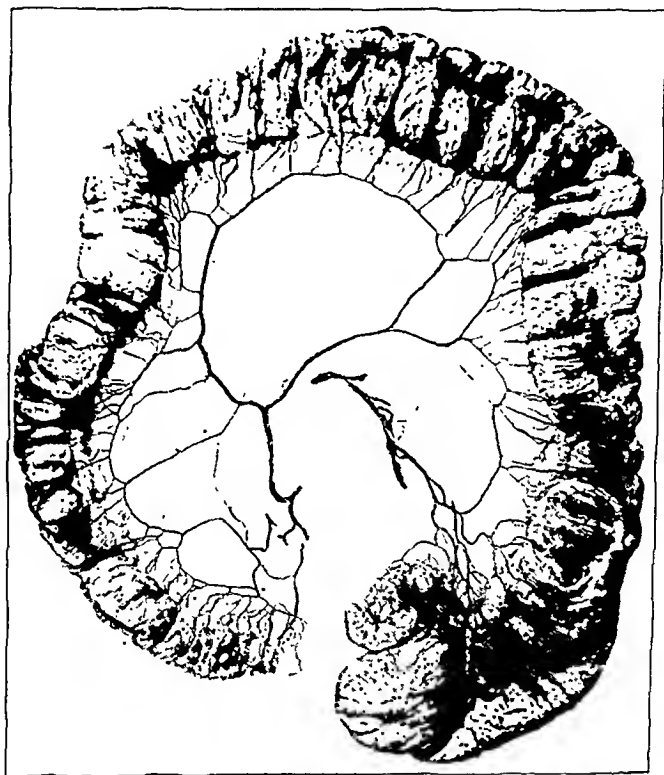
Fig. 5.—Posterior view of celluloid cast of a specimen showing: (1) the anterior cecal branch (broken) as the first branch of the ileocolic artery, and (2) the absence of the middle and right colic arteries, replaced by the left colic artery.

between the layers of the mesocolon, then divides, its branches supplying the transverse colon and anastomosing with the right and left colic arteries. Some remarkable variations of the middle colic artery have been reported. Sappey[61] stated that the middle colic artery is often absent. Henle described branches of the superior and inferior mesenteric arteries replacing the middle colic, and it is Hyrtl's belief that it

61. Sappey, M. P. C.: Traité d'anatomie descriptive; avec figures intercalées dans le text, ed. 3, Paris, V. A. Delahaye et Cie, 1876, vol. 2, p. 556.

may be replaced by omental branches. Henle reported a case of two middle colic arteries, and Waldeyer described an accessory middle colic artery occasionally arising before the middle colic artery and coursing to the left. Moynihan[62] occasionally found an accessory middle colic artery running directly toward the middle of the transverse colon, and Jamieson and Dobson[60] noted its occasional occurrence.

In this study, the variations of the middle colic artery were confirmed. The point of bifurcation of the artery was from 3 to 11 cm. from the wall of the colon, but usually it divided between 5 and 7 cm.
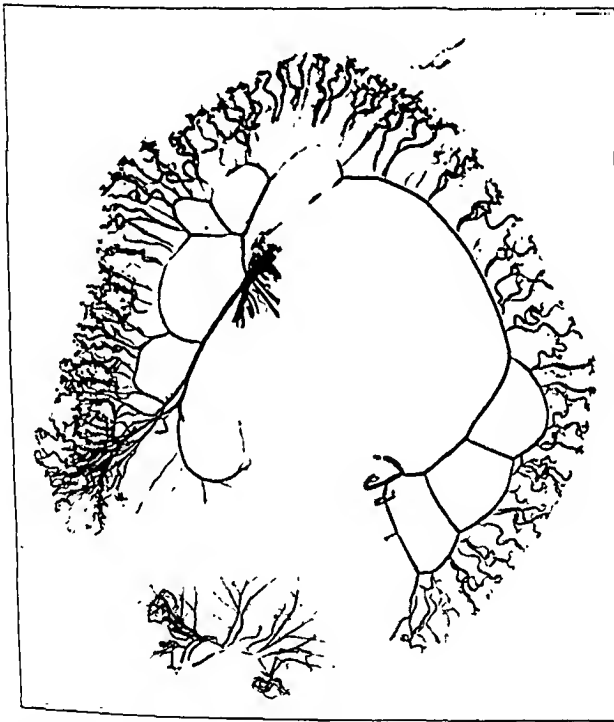
Fig. 6.—Specimen injected with opaque mixture showing: (1) the anterior cecal artery as the first branch of the ileocolic artery; (2) multiple ascending colic branches from the anterior cecal branch, and (3) the origin of the right colic from the ileocolic artery.

As a rule, the larger the artery and its branches, the greater the distance between the point of bifurcation and the wall of the colon. In all cases the artery began its course to the right, and usually only a part of one branch passed to the left of the median line of the body. Usually there were two branches of the middle colic artery (fig. 7), but trifurcation of the artery was not unusual (fig. 8) and as many as four

62. Moynihan, Berkeley: The Cavendish Lecture, Being Remarks on the Surgery of the Large Intestine, Lancet **2:**1 (July 5) 1913.

branches were sometimes found (fig. 9). In 27 per cent of the specimens a large branch of the middle colic artery ran toward the splenic flexure and reinforced the marginal artery near that point (figs. 9 and 10). In 10 per cent of the specimens an accessory middle colic artery was found arising from the superior mesenteric artery above the origin of the middle colic artery, running to the left in the mesocolon and anastomosing with the marginal artery near the splenic flexure (fig. 11). In two specimens (5 per cent of the series) the middle colic artery was entirely absent and was replaced by a large branch from the left colic artery (fig. 5).
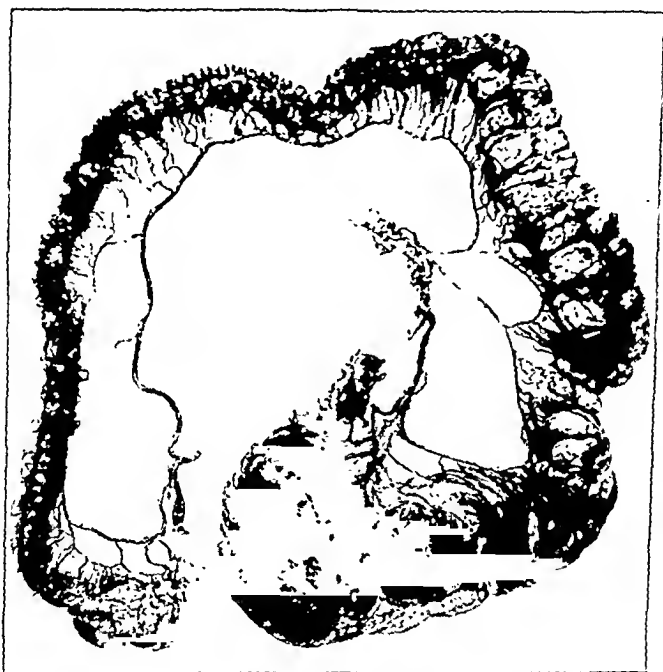
Fig. 7.—Posterior view of a celluloid cast of a specimen showing: (1) the origin of the right colic from the superior mesenteric artery; (2) the middle colic artery dividing into two large branches, and (3) the left colic artery passing above the splenic flexure to the transverse colon.

It may be concluded that the middle colic artery does not occur constantly, that it varies in the number of branches, and through large branches, or by accessory middle colic arteries it supplies the left side of the transverse colon and splenic flexure in 37 per cent of the cases.

The left colic artery is described as the first branch of the inferior mesenteric artery. It passes transversely to the left and divides into an ascending branch and a descending branch which supply the descending colon and anastomose respectively with the left branch of the middle colic artery and the first sigmoid artery. There is some confusion among the older anatomists concerning the names applied to the left colic artery.

As late as 1844, Cruveilhier referred to two or three left colic arteries, and Sappey, in naming the left colic artery, preferred to call all other branches of the inferior mesenteric artery, hemorrhoidal branches. This confusion was probably a result of designating the sigmoid as part of the descending colon, and the variation in the number of sigmoid arteries.

In this study the left colic artery was present in every specimen. The distance of the point of bifurcation from the wall of the colon varied from 3 to 10 cm. The course of the artery and its branches was extremely variable: In 27 per cent of the cases the ascending branch
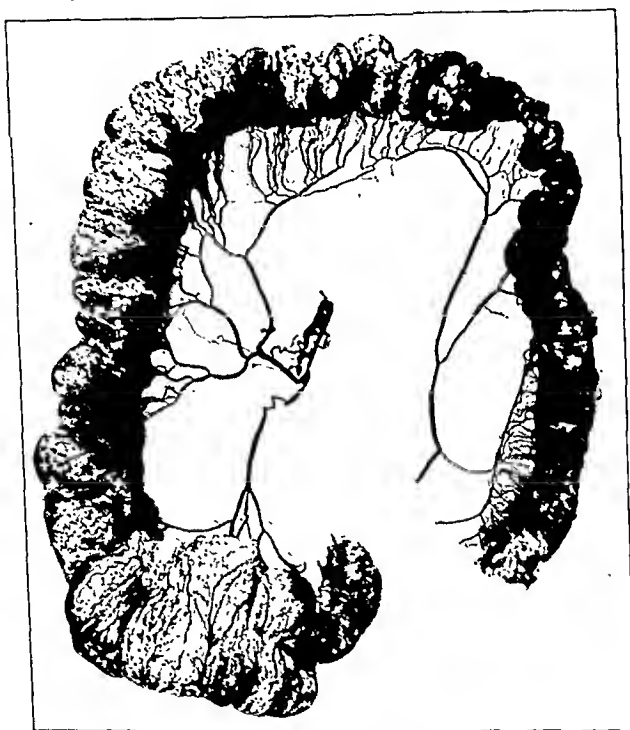
Fig. 8.—Celluloid cast of a specimen showing: (1) trifurcation of the middle colic artery and (2) anastomosis between the left and middle colic arteries effected by a slender branch.

did not extend to the splenic flexure (figs. 9 and 10), and in 63 per cent it passed above the flexure and supplemented the marginal artery in the region of the left transverse colon (figs. 7 and 8). In this last type of case the ascending branch was larger than the descending one and frequently had several branches connecting it with the marginal artery which lay close to the bowel (fig. 3). In these cases the ascending branch of the left colic artery served as a large and more distally situated second marginal artery. One specimen in which the mesocolon was "M" shaped had a large secondary anastomosing loop
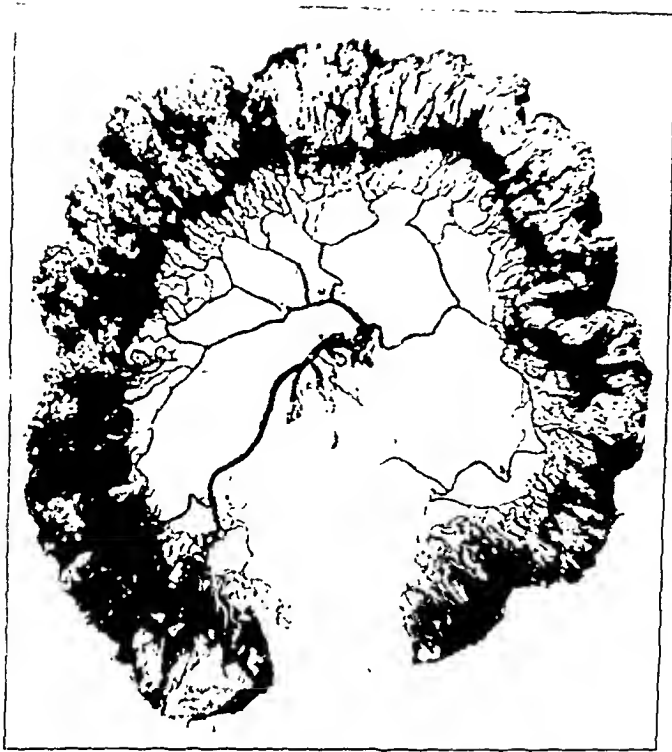
Fig. 9.—Celluloid cast of a specimen showing: (1) the middle colic artery with four branches; (2) the left colic artery going to the descending colon below the splenic flexure, and (3) a few tertiary loops along the marginal artery.
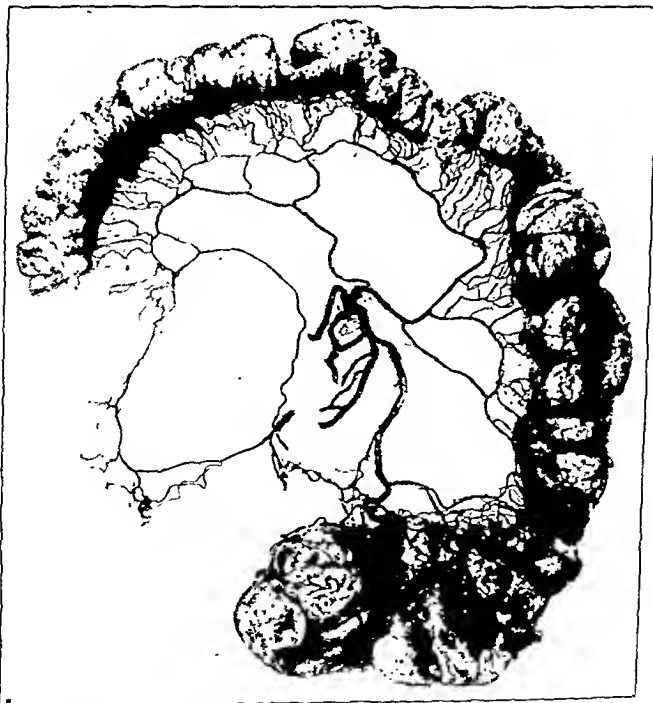
Fig. 10.—Posterior view of a celluloid cast of a specimen in which a branch of the middle colic courses toward the splenic flexure.

between the left and middle colic arteries and a smaller anastomosis between the left colic and superior mesenteric arteries (fig. 12). Both of these loops were short and sutured close to the base of the mesentery of the small intestine. The entire blood supply of the specimen was distorted by the deficiency in the mesocolon, although embryonic rotation appeared to have been normal.

It may be concluded that there is marked variation in the size, course and distribution of the branches of the left colic artery, and that
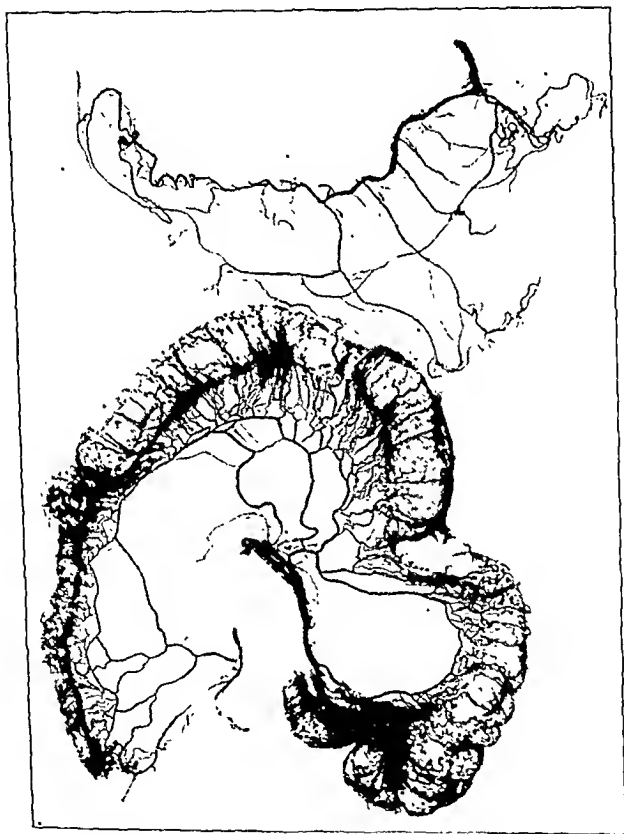
Fig. 11.—Posterior view of a celluloid cast of a specimen including injection of arteries of the omentum showing: (1) the accessory middle colic artery and (2) the left colic artery coursing to the descending colon below the splenic flexure.

in most cases the ascending branch extends above the splenic flexure to the transverse colon.

Marginal Arteries: The first comprehensive description of the blood supply of the colon by von Haller drew attention to the anastomosis of the adjacent colic arteries near the wall of the bowel. Since von Haller's description, anatomists have acclaimed the significance of the anastomosis along the wall of the colon as the only connection

between the superior and inferior mesenteric arteries. If the anastomosing loops are considered as an entity, the main colic branches may be considered simply as the source of supply for this artery.

Although the existence of the arterial arcade along the colon has long been recognized, descriptions by anatomists have been meager. This neglect may be due to the variations of the arcades. Von Haller stated that the arches are fewer and less often subdivided than in the small intestine, and that the trunks of the arches follow the course of the bowel. Cruveilhier described the structure as large arterial arches with their convexity near the bowel. Henle, Quain and Piersol only stated that the anastomosing branches run near the bowel. Gray placed
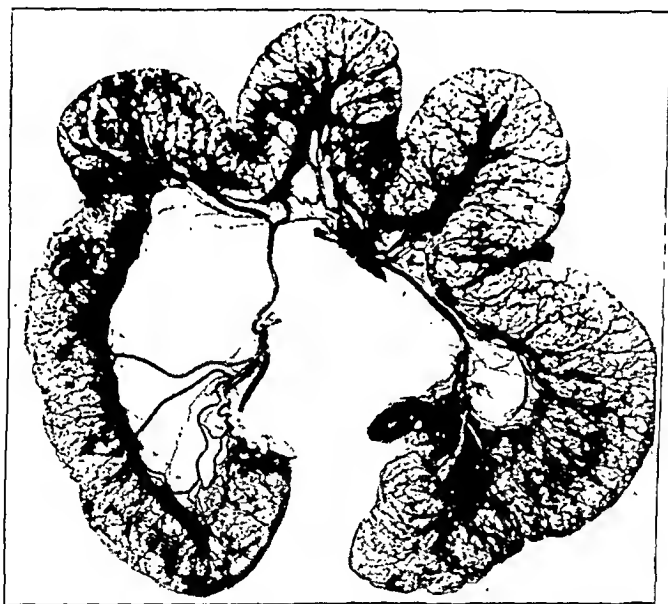
Fig. 12.—Posterior view of a celluloid cast of a specimen with "M" shaped transverse mesocolon showing secondary anastomosis between the left and middle colic arteries: *a,* small connecting branch between the left colic and superior mesenteric arteries.

the artery two fingerbreadths from the transverse colon. Hyrtl called attention to secondary and even tertiary arches in the angles of the flexures, and Jamieson and Dobson [60] stated that secondary and tertiary arches are not common.

Okinczyc [63] described multiple arcades at the angles of the colon and stated that they are more common at the splenic than at the hepatic flexure.

The continuity of the anastomosing arcades is not accepted unquestioningly. Okinczyc stated that the anastomosis between the arteries

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63. Okinczyc, J.: Anatomine chirurgical des colons, in Hartmann, Henri.[58]

to the right and transverse portions of the colon is often slender. Merkel wrote that the anastomosis between the middle and left colic arteries may fail, and Cunningham, in considering the failure, called attention to the fact that in ruminants and some rodents there is no anastomosis between the mesenteric arteries. Among writers on surgical subjects, Lockhart-Mummery[64] mentioned occasional failure of anastomosis of the left and middle colic arteries.

With the growth of surgery, the significance of the anastomosis of the colic arteries has become more apparent. Litten,[65] in 1875, found that the anastomosis with the inferior mesenteric artery was not sufficient to prevent gangrene of the colon of dogs if the superior mesenteric artery was ligated. Morestin,[66] in 1893 (quoted by Archibald), reported that the inferior mesenteric artery in dogs might be ligated and circulation of the lower part of the bowel maintained. Archibald,[67] in 1908, substantiated the experiments of Morestin and also found that material injected into the superior mesenteric artery of cadavers would progress to the hemorrhoidal arteries when all branches of the inferior mesenteric artery were ligated some distance from the wall of the colon. Sudeck,[68] in 1907, studying the blood supply of the lower part of the colon by injection and roentgenologic examination, and Rubesch,[69] in 1910, writing on gangrene of the rectum after operations, drew attention to the importance of the artery running near the wall of the bowel. Drummond,[70] in 1913, presented evidence of the importance of the anastomosis of the colic arteries. In several postmortem investigations he tied all the main arteries of the colon and sigmoid near their origins, and found that the sigmoid vessels could be filled with material injected into the ileocolic artery. Drummond first used the term "marginal artery" in referring to the anastomosing arches along the wall of the colon. Rothschild[71] recently concluded, from animal experimentation, that severance of the mesentery of the

64. Lockhart-Mummery, Percy: Diseases of the Rectum and Colon and Their Surgical Treatment, London, Baillière, Tindall & Cox, 1923.

65. Litten, M.: Ueber die Folgen des Verschlusses der Arteria mesaraica superior, Virchows Arch. f. path. Anat. **63**:289 (May 25) 1875.

66. Morestin, quoted by Archibald.[67]

67. Archibald, Edward: Operative Treatment of Cancer of the Rectum, J. A. M. A. **50**:573 (Feb. 22) 1908.

68. Sudeck, P.: Ueber die Gefässversorgung des Mastdarmes in Hinsicht auf die operative Gangrän, München. med. Wchnschr. **2**:1314 (July 2) 1907.

69. Rubesch, R.: Ueber die Vermeidung der Darmgangrän bei Rectumoperationen, Beitr. z. klin. Chir. **67**:480, 1910.

70. Drummond, Hamilton: Some Points Relating to the Surgical Anatomy of the Arterial Supply of the Large Intestine, Proc. Roy. Soc. Med. (Sect. Proct.) **7**:185, 1914.

71. Rothschild, N. S.: Safety Factors in Mesenteric Ligations, Ann. Surg. **89**:878 (June) 1929.

large bowel which permits the marginal artery to be left intact does not interfere with the viability of the bowel. At present, in spite of the reported failures of anastomosis between the colic arteries and the protests of Desmarest,[72] and Jamieson and Dobson, surgeons successfully ligate individual colic arteries as the occasion demands and rely on vascularization through the marginal artery.

Study of the marginal artery in the injected specimens emphasized its value as a source of blood supply to the colon. The marginal artery was continuous from the ascending colon to the sigmoid in all but 5 per cent, and in these there was failure of anastomosis between the ileocolic and the right colic arteries (fig. 2). In several other specimens this anastomosis was slight (fig. 4); however, this appeared to be evidence of profuse supply to the part rather than of avascularity, as there were large, independent branches of the cecum and ascending colon.

In all of the specimens there was union of the left colic and middle colic arteries. This fact deserves particular emphasis because of the prevalent, hazy statements to the contrary. One of us (Dr. Rankin[73]) incorrectly wrote that the anastomosis occasionally fails to exist and this opportunity is taken to correct the statement. In more than a hundred specimens in which this particular area was examined there was no failure of anastomosis of the middle and left colic arteries. The only specimen which suggested this possibility was one (fig. 8) in which the left and middle colic arteries were large, and the anastomosis was affected by an unusually slender branch, which may have been the result of an artefact in the preparation or injection of the specimen.

The distance of the marginal artery from the wall of the colon is inconstant. A general estimate should not be made as the distance varies in each specimen, and in the different parts of the same specimen, from a fraction of 1 to 8 cm. As a rule, the artery is farthest from the wall at the points of bifurcation of the main arteries; the larger the marginal artery at a particular point, the more distant it is likely to be from the bowel. Usually the marginal artery is nearer the left half of the transverse and the descending portion of the colon than the right half of the colon.

The secondary arcades are also inconstant. They are most common at the points of bifurcation of the main arteries or their subdivisions, but there is no regularity in their presence. Tertiary loops are occasionally found, but never in the number or frequency suggested by

72. Desmarest, E.: Technique de la résection de l'angle gauche du colon pour cancer, J. de chir. **14**:575, 1917-1918.

73. Rankin, F. W.: Surgery of the Colon, New York, D. Appleton and Company, 1926.

Sharpe,[74] who described a dichotomous distribution of the arteries of the colon. Secondary loops give a more flexible blood supply to a colon, but their existence is not constant enough so that the surgeon may safely place any degree of reliance on them.

It may be concluded that a marginal artery occurs quite constantly, failing only in rare cases along the ascending colon in the presence of a profuse supply from direct branches; that it runs at varying distances from the wall of the colon, and that it may have secondary loops in different positions in its course.

Terminal: The terminal vessels of the colon have not been fully described. Von Haller gave one of the earliest and best descriptions: " . . . the branches on the intestines less arbuscular (than in the small intestine), divided at less angles and more tortuous; and the reticulation in the cellular substance is lower." Henle simply stated that the arches give direct branches to the colon without further anastomosis and the branches run in the haustra. Sobotta stated that a number of the branches irregularly anastomose before they enter the wall of the colon. Piersol described irregular twigs passing to the colon, and Gray and Cunningham stated that branches are distributed to the colon by the loops formed by the branches of the colic arteries.

The terminal arteries of the colon are not described by histologists. Bailey, Böhm,[75] Jordan, and Lewis and Stöhr [76] described the vessels after they enter the intestinal wall but did not mention their course proximal to that point.

The terminal arteries of the colon have been most thoroughly described by surgeons. Drummond,[77] writing on diverticula of the colon, Meillere [78] on the epiploic appendages, and Fischer,[79] looking for cause of gangrene in ·operating on the colon, fully described the course of these arteries. Eisberg [80] called attention to the difference in

74. Sharpe, N. W.: The Arcuate Distribution of Arteria Mesenterica Superior and Arteria Mesenterica Inferior: Surgical Significance in Intestinal Resections, Interstate M. J. **20**:1152 (Dec.) 1913.

75. Böhm, A. A.: Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1900.

76. Lewis, F. T., and Stöhr, Philipp: A Text-Book of Histology, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1913.

77. Drummond, Hamilton: Sacculi of the Large Intestine, with Special Reference to Their Relations to the Blood Vessels of the Bowel Wall, Brit. J. Surg. **4**:407, 1917.

78. Meillere, J.: Étude de la vascularisation des tuniques du segment gauche du colon et ses applications chirurgicales, Ann. d'anat. path. **4**:867 (Nov.) 1927.

79. Fischer, A. W.: In wie weit ist durch die Ablösung des Dickdarmfettbehanges der Sicherheit der Dickdarmnaht gefährdet? Arch. f. klin. Chir. **152**:638, 1928.

80. Eisberg, H. B.: On the Viability of the Intestine in Intestinal Obstruction, Ann. Surg. **81**:926 (May) 1925.

position of the vasa recti as they pierce the wall of the small intestine and of those that pierce the wall of the colon.

The branches of the terminal arteries usually originate independently from the marginal artery and proceed directly to the colon, but occasionally two branches may have a common origin. Anastomosis between terminal branches before they reach the colon is rare. Terminal arteries are most numerous in the cecum and ascending colon. The size of the terminal arteries in the transverse and descending colon is slightly smaller, and the number of vessels per centimeter is less than in the ascending portion. The branches vary slightly with the size of the subject, but there is no difference in the size of the arteries in the dilated and the contracted portions of the colon in the same specimen.
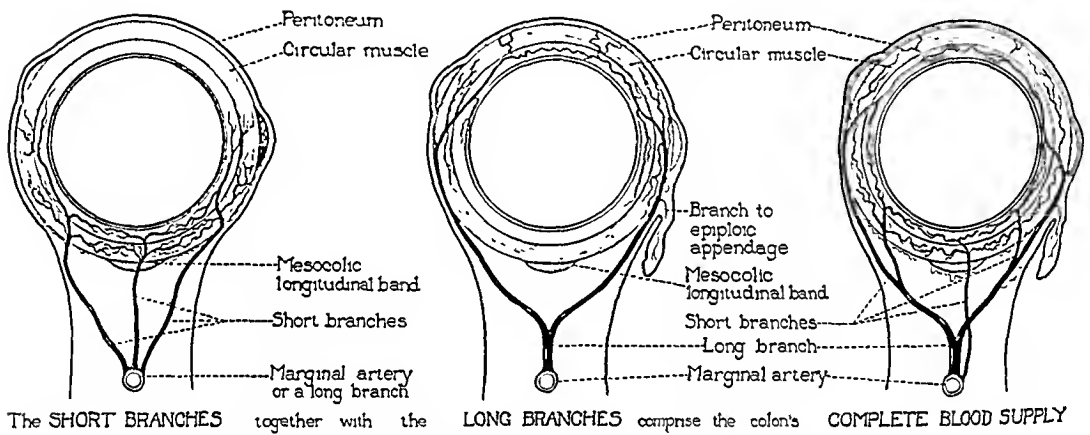
Fig. 13.—Diagram of the terminal arteries of the colon; *a*, long branches; *b*, short branches, and *c*, complete supply by both long and short branches.

The terminal arteries to the colon are of two types: long and short branches, a combination of the two types affecting the complete supply to the wall (fig. 13). The long branches divide near the mesocolic taenia, one branch courses in the haustra on the anterior aspect, and the other on the posterior aspect of the wall of the colon. In this part of their course the arteries lie in the serosa and give off short branches to the mesocolic portion of the colon, small twigs to the serosa and peritoneum and arteries to the epiploic appendages.

Near the amesocolic or distal longitudinal bands the long branches divide and pass deeply beneath the longitudinal muscle and through the circular muscle to the submucosa. In this position they continue their course, sending small branches upward to the muscle and peritoneal covering. In the submucosa anastomosis is established with the short branches and a relatively scanty anastomosis with the long branch from the opposite side of the colon (fig. 14).

The short branches of the terminal arteries to the colon may originate from the marginal artery, but the majority are given off by the long branches. The short arteries are smaller and about four or five times as numerous as the long branches. The first short branches to arise pierce the mesocolic longitudinal band, giving twigs to serosa and muscle in passing, and go directly to the submucosa. The other short branches lie loosely in the serosa where they appear tortuous and anastomose through fine serosal twigs. The branches then pass through the circular muscle to the submucosal plexus at various points. The large number of short branches gives the mesocolic arteries of the colon a preponderance of the blood supply. The general course

Fig. 14.—Dissection of a long terminal artery to the colon showing: (1) vessels to the serosa and epiploic appendage; (2) the long artery coursing through the circular muscle and beneath the amesocolic longitudinal band to divide in the submucosa, and (3) the submucosal anastomosis with the vessels from the opposite side of the colon.

of the terminal arteries to the colon is perpendicular to the axis of the bowel with little lateral anastomosis. This arrangement is obvious in roentgenograms of a segment of colon injected with opaque material. When an injected segment of colon is compared with a segment of injected jejunum from the same case, more acute angulation and profuse lateral anastomosis of the arteries in the wall of the small bowel are seen.

Regarding the terminal arteries of the colon, it may be concluded that: (1) they are of two types, long branches which supply the amesocolic or distal third of the colon, and short branches which supply the mesocolic or proximal two thirds of the colon; (2) the mesocolic taenia

portion of the colon has most of the blood supply; (3) the course of the terminal arteries is in general perpendicular to the axis of the bowel, and (4) there is little anastomosis between the terminal vessels except in the submucosa.

Arterial Pattern.—The blood supply of the colon, composed of the main colic arteries and the marginal artery, should now be considered. An interesting variety of patterns was found in the specimens, no two of which were alike. The arteries and their branches varied in size and distribution. They were usually unequal and supplied lengths of the colon corresponding to their size. When one artery was large, the adjacent arteries were likely to be smaller than normal. Because of branches from the middle colic artery passing to the left, the existence of an accessory middle colic artery in 10 per cent of cases and the frequency with which the left colic artery passes above the splenic flexure, the long single arcade customarily described as the anastomosis between the middle colic and left colic arteries is usually reduced in length.

A substantiation of the varying distribution of the colic arteries is supplied by postmortem observations in cases of thrombosis of the mesenteric vessels. Trotter [81] reviewed two cases of complete occlusion of the inferior mesenteric artery, in both of which the entire descending colon was involved. Contrasted with these two cases was one reported by Parker [82] in which there was complete occlusion of the inferior mesenteric artery with gangrene beginning in the lower half of the descending colon. Similarly, the extent of intestinal involvement varied in complete thrombosis of the superior mesenteric artery. Trénel [83] and Cénac reported involvement of the entire colon in complete thrombosis of the superior mesenteric artery, and Frank [84] observed that exploration in such cases may reveal the entire large intestine to be gangrenous. Compared with these observations is a recent case at the Mayo Clinic [85] in which there was complete occlusion of the superior mesenteric artery and a sharp line of demarcation at the hepatic flexure with viable intestine beyond this point. The only conclusion possible from a review of these cases is that the arteries supplied varying lengths of colon.

81. Trotter, L. B. C.: Embolism and Thrombosis of the Mesenteric Vessels, New York, Cambridge University Press, 1913.

82. Parker, C. B.: Mesenteric Thrombosis with Report of Two Cases, Canad. M. A. J. **12**:655 (Sept.) 1922.

83. Trénel and Cénac: Thrombose de l'artère mésentérique supérieure, Bull. et mém. Soc. anat. de París **92**:406 (Nov.) 1922.

84. Frank, Louis: Mesenteric Vascular Occlusion: Report of Three Cases in Children, Am. J. Surg. **37**:304 (Dec.) 1923.

85. Steward, J. A.: Unpublished data.

ANASTOMOSIS OF ARTERIES BETWEEN THE OMENTUM AND COLON

Von Haller described the omental as well as the intercostal, lumbar and spermatic arteries as furnishing small arteries to the colon. A century later Hyrtl [16] emphasized the idea of anastomosis between the vessels of the colon and omentum when he found that material injected into the gastro-epiploic arteries filled the middle colic artery. He concluded that the anastomosis of the omental arteries with those of the colon might replace an absent middle colic artery. Later, Cruveilhier, Gray, Cunningham and Piersol stated that the transverse colon receives its blood supply from the omental arteries.

Surgeons have not verified the anastomosis between the arteries of the omentum and those of the colon. Lardennois and Okinczyc [59] stated that twigs do not exist which merit a ligature when the omentum is separated from the colon, and W. J. Mayo [86] found that only one artery near the splenic flexure need be tied in separating the two structures. Lardennois [87] pointed out that all important vessels of the omentum run on the anterior layer.

It has been shown that in the embryonic state the vessels of the colon have been formed before the omentum fuses to the transverse colon. Because of this fact and the discrepancy between surgical and anatomic observations, particular effort was made in this study to determine the amount of anastomosis between the vessels of the omentum and the colon. The omentum was left attached to the colon in all injected specimens. In two specimens used for injection of celluloid the gastro-epiploic arteries were carefully prepared and injected with a different colored celluloid solution for several hours before the superior mesenteric artery was injected.

The specimens we injected for roentgenologic study disclosed only occasional small branches in the attached omentum, although other arteries of very small caliber were well injected. In the series of injections of celluloid the omental arteries did not fill, and twigs longer than those to the peritoneum were not seen. In the two specimens in which the gastro-epiploic arteries were injected, two small branches were seen connecting the transverse colon with the omentum. The anterior arteries of the omentum became very small near the free edge, and although anastomosis between the small posterior arteries of the omentum and the terminal arteries to the colon is established, the connecting vessels were found to be peritoneal twigs from the long branches of the terminal arteries (fig. 11).

86. Mayo, W. J.: Radical Operations for the Cure of Cancer of the Second Half of the Large Intestine, Not Including the Rectum, J. A. M. A. **67**:1279 (Oct. 28) 1916.

87. Lardennois, G.: Colectomie totale et colectomie sous-caecale, Technique opératoire, J. de chir. **12**:701, 1914.

It may be concluded that the anastomosis between the arteries of the omentum and the transverse colon is normally through a few branches from the terminal arteries of the colon, and that the anastomosing branches are about equal in size to large peritoneal twigs.

Veins.—As a corollary of the arterial circulation, it would be well at this point to describe the venous return of the blood from the colon. Early in our study special attention was given to veins of the colon, and a celluloid cast was made of both the arteries and veins, red and blue coloring material, respectively, being used in the two systems. Unfortunately, the large veins were difficult to fill and were broken in the attempt to photograph the resulting specimen.

It may be stated in general that the veins of the colon follow directly the course of the corresponding arteries. The left colic vein is an exception to this and will be considered later. The small veins from the wall of the colon to the marginal vein are of two types, the short and the long, as in the case of the arteries. Their general course is the same as that of the arteries, but there are always at least two veins for each artery. Whether this is a result of a physiologic demand due to absorption of liquid in the colon, or to the fact that the thin-walled veins are easily compressed by peristaltic movements of the colon so that more are needed, is a matter of conjecture.

The marginal vein of the colon follows closely the marginal artery in its formation and distribution, lying as a rule posterior and slightly mesial to the artery. From the marginal vein the subdivisions and principal branches parallel the course of the arteries, which form the general pattern, and empty into the superior mesenteric vein.

The left colic vein is a distinct exception to this orderly return of the colic veins along the arterial courses. It is formed by branches corresponding to the divisions of the left colic artery and unites with the inferior mesenteric vein. This union is lateral to the point of division of the arteries and the vein takes an upward course for several centimeters before curving mesially above the jejunoduodenal juncture to empty into the superior mesenteric vein. The termination of the inferior mesenteric vein is said to be often into the splenic vein; however, the opening is so close to the superior mesenteric vein that for all practical purposes this may be considered its termination.

Summary.—In studying the blood supply of the colon we removed the entire colon with its vessels and peritoneal attachments. The arteries of the specimens were injected with celluloid mixture and corroded, or with an opaque material and roentgenograms made. The vessels of forty such specimens were observed. The inferior and superior mesenteric arteries were always present and do not appear to anastomose with arteries of other viscera. The colic arteries vary in course, branching and distribution. The marginal artery is constantly

present, but runs at varying distances from the wall of the colon. The terminal arteries of the colon pursue a course different from those of the small intestine, are of two types, have little lateral anastomosis and furnish the mesocolic taenia portion of the colon more profusely than the distal part. There is only slight peritoneal anastomosis between the omentum and the transverse colon.

THE SIGMOID

Continuing downward, the descending colon becomes the sigmoid or pelvic colon. The exact point of transition is differently stated, either opposite the crest of the ilium or at the upper border of the psoas muscle. The structure of the bowel does not vary from that of the descending colon, although the diameter may be greater or smaller. This part of the large bowel is usually attached by a mobile mesentery or mesosigmoid to the posterior wall. Treves found that the length of the sigmoid varies from 15 to 71 cm., averaging 43 cm., and that the mesosigmoid is 7 cm. in length at the base and is from 10 to 20 cm. in width.

The arteries to the sigmoid usually arise from the lateral aspect of the inferior mesenteric artery and spread fanlike in the mesosigmoid toward the bowel (fig. 15), supplying not only the sigmoid, but in cases in which the left colic artery is small or has a high course, the lower part of the descending colon as well. The number of sigmoid arteries varies; Rubesch stated that there may be from one to nine and Pope and Judd, one to four. Drummond[88] found that the first sigmoid artery was given off by the left colic artery in more than 50 per cent of twenty cases studied, and it is not unusual to find all of the sigmoid branches arising from this vessel. The arteries divide and may undergo several subsequent subdivisions before reaching the marginal artery. The arterial branches anastomose with those in their vicinity to form a network in the mesosigmoid, ramifying the marginal artery. Pope and Judd called attention to these variations of arterial pattern in the mesosigmoid. There may be as many as four arcades in the arterial pattern of the sigmoid, and the number of vascular arches is apparently independent of the length and mobility of the mesosigmoid. The marginal artery, which is continuous with that of the descending colon, may lie from a fraction of a centimeter to several centimeters from the sigmoid wall. The distance of the marginal artery from the wall, as in the case of the colon, has no relation to the length of the mesosigmoid.

From the marginal artery of the sigmoid the terminal arteries are sent to the wall of the bowel. These are similar in kind (long and

88. (a) Drummond, Hamilton: The Arterial Supply of the Rectum and Pelvic Colon, Brit. J. Surg. **1**:677, 1914.   (b) Drummond.[70]

short) and course to those of the colon. Frequently in the lower por-
tion of the sigmoid and sometimes in the middle portion the longitudinal
fibers spread outward from the longitudinal bands and form a complete
investment of the bowel. In such cases the long arteries pass beneath
the longitudinal fibers near the mesosigmoid portion of the bowel. The
veins follow the general course of arteries in all the smaller ramifications
until the large veins are formed. These take an upward course, uniting
near the base of the mesosigmoid, finally joining with the left colic
from the inferior mesenteric vein.
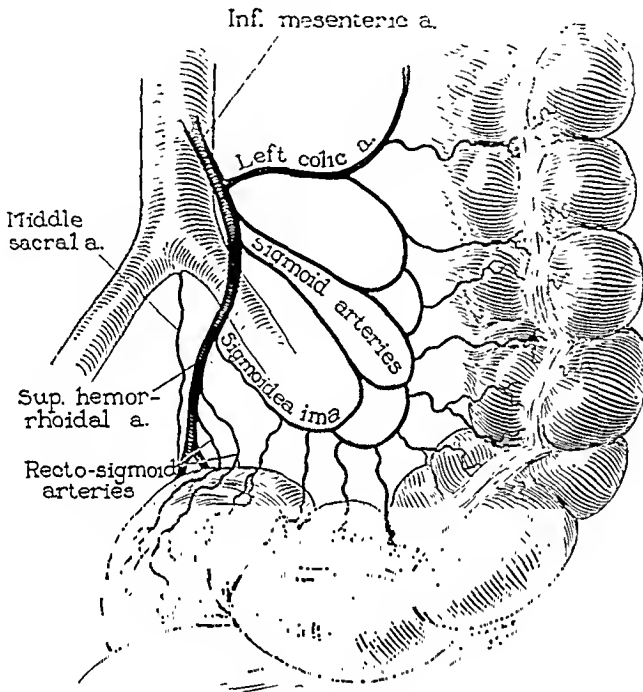
Fig. 15.—Arteries to the sigmoid and rectosigmoid.

THE RECTOSIGMOID

The portion of the large intestine at the juncture of the sigmoid and
rectum has long been of particular anatomic and surgical interest, both
as regards the bowel and its blood supply. In this region the longi-
tudinal bands of muscle spread to form a complete coat ; the mesosig-
moid is at first markedly shortened, and a few centimeters farther it
disappears entirely, leaving the bowel with peritoneum on the anterior
surface only. In the last few decades this region has been referred
to as the rectosigmoid, and although the term is anatomically descriptive,
it is necessarily loosely used because of the variation in position and
length of the two parts involved. The point at which the sigmoid ends
and the rectum begins has been widely discussed. Gibson,[89] in 1697,

89. Gibson, quoted by Jones.[99]

said: "This hath its beginning at the first vertebra of the os sacrum." Treves, in 1885, located the beginning of the rectum opposite the third sacral vertebrae and assigned the upper portion to the pelvic colon. Jonnesco,[90] in 1889, confirmed Treves' observations, and since then anatomists for the sake of exactness have adopted the third sacral vertebra as a convenient landmark for defining the upper end of the rectum. In texts on surgery of the rectum writers are in the habit of quoting different figures as to the length of the rectum. Yeomans,[91] and also Edwards,[92] stated that the rectum is from 12 to 15 cm. in length; Pennington[93] gives the length of from 13 to 16 cm.; Cripps[94] from 15 to 20 cm., and Tuttle[95] from 9 to 15 cm. The length is greater in males than in females, greater in the aged than in the young, and it may be increased at any time by distention. Other methods of determining the upper limit of the rectum are also inexact. Gant[96] uses the third, or O'Beirne's sphincter, to define the juncture of the rectum and sigmoid, but Symington[97] doubted the existence of such a structure, and Hyrtl,[98] although believing in the sphincter physiologically, was often unable to demonstrate it in carefully executed dissections. Again, attempts have been made to determine the upper limit of the rectum by means of Houston's valves. Jones,[99] as well as Patterson,[100] advocated the use of the third valve of Houston, or the superior rectal fold, as the upper limit of the rectum. These folds are admittedly variable in form and position and are of no value as landmarks except when seen through a proctoscope.

90. Jonnesco: Note sur l'anatomie de l'iliaque, Bull. Soc. anat. de Paris **3**:232 (March) 1889.

91. Yeomans, F. C.: Proctology, New York, D. Appleton and Company, 1929.

92. Edwards, F. S.: Diseases of the Rectum, Anus and Sigmoid Colon, ed. 3, London, J. & A. Churchill, 1908.

93. Pennington, J. R.: A Treatise on the Diseases and Injuries of the Rectum, Anus and Pelvic Colon, Philadelphia, P. Blakiston's Son & Co., 1923.

94. Cripps, W. H.: On Diseases of the Rectum and Anus, London, J. & A. Churchill, 1913.

95. Tuttle, J. P.: A Treatise on Diseases of the Anus, Rectum and Pelvic Colon, New York, D. Appleton and Company, 1906.

96. Gant, S. G.: Diseases of the Rectum, Anus and Colon, Philadelphia, W. B. Saunders Company, 1923.

97. Symington, J.: Further Observations on the Rectum and Anal Canal, J. Anat. & Physiol. **46**:289 (April) 1912.

98. Hyrtl, Joseph: Lehrbuch der Anatomie der Menschen mit Rücksicht auf physiologische Begründung und praktische Anwendung, Vienna, Wilhelm Braumüller, 1889.

99. Jones, F. W.: The Delimitation of the Rectum and Its Subdivisions, Proc. Roy. Soc. Med. (Surg. Sect.) **4**:85, 1911.

100. Patterson, A. M.: The Form of the Rectum, J. Anat. & Physiol. **43**:127 (Jan.) 1909.

Not only is it difficult to establish the upper limit of the rectum, but also that of the sigmoid, which varies in its position. The study by Bourcart [101] of the sigmoid of children gives a developmental background for the varying positions noted by practically all anatomists. Treves called attention to the frequency of morbid contractions and adhesions of the mesosigmoid, and Sappey warned [20] observers that the direction of the sigmoid presents many variations. Buie [102] called attention to the frequency with which the opening into the sigmoid is seen through the proctoscope to be on the right rather than the left side. From a review of the anatomic peculiarities of the region, we concluded that the point at which the sigmoid joins the rectum may vary appreciably in length.

Below the level of the left common iliac artery, the inferior mesenteric artery, lying in the base of the mesosigmoid, becomes the superior hemorrhoidal artery. The artery proceeds toward the median line and downward to its point of bifurcation. The point of bifurcation is generally said to be at the third sacral vertebra and is one of the criteria used to determine the upper end of the rectum. However, the point of bifurcation is in some dispute. Cripps found that the artery divides from 10 to 11 cm. above the anus, whereas Rubesch gives the point of division at from 17 to 20 cm. from the anus. Lockhart-Mummery's observation that the point of division of the superior hemorrhoidal artery varies considerably, as a rule at the upper end of the rectum, but that it is not rare to find a low bifurcation, seems most logical.

The branches of the superior hemorrhoidal artery in its short course from its beginning at the level of the left common iliac artery to its bifurcation have been extensively studied. In the ordinary case the branches generally consist of a vessel which sends a branch upward along the pelvic sigmoid to anastomose with the last sigmoid artery and several (from two to four) branches which run downward more or less parallel with the bowel.

Because of the mechanical difficulties encountered in this region and the frequent occurrence of gangrene following surgical procedures, the anastomosing artery from the superior hemorrhoidal to the sigmoid has commanded considerable attention. Numerous studies of the vessel have been made by injection. Sudeck, in 1907, was the first to emphasize the anastomotic value of the vessel. He found that the vessels of the rectum became filled with injected material from the inferior mesenteric artery by traversing the marginal artery when a ligature was placed on the superior hemorrhoidal artery above the origin of the

101. Bourcart, quoted by Tobias, Milton: Sigmoid Flexure in Constipation in Children: Preliminary Report, Am. J. Surg. **13**:301 (Aug.) 1931.

102. Buie, L. A.: Proctoscopic Examination and the Treatment of Hemorrhoids and Anal Pruritus, Philadelphia, W. B. Saunders Company, 1931, p. 45.

last branch to the sigmoid. If the ligature were placed below the origin of the artery, few if any of the rectal vessels were injected. Sudeck therefore established the origin of the last sigmoid artery as the critical point for maintaining the blood supply to the rectum in cases in which it was necessary to ligate the superior hemorrhoidal artery to obtain mobility. This experiment was substantiated by Hartmann [28] two years later. However, Rubesch, in 1910, studying this region by the same method, called attention to the fact that the last sigmoid artery, which he calls the sigmoidea ima, may be given off below the bifurcation of the superior hemorrhoidal artery, and that the so-called critical point is not exactly situated but may be encountered within a range of from 13 to 20 cm. from the anus. Manasse [103] emphasized the feebleness of the border vessel in the lower portion of the sigmoid and stated that the last sigmoid artery does not participate in it to a great extent. Drummond,[104] in 1914, studied by injection and roentgenograms the inferior mesenteric artery of twenty specimens. The results of this work are convincing. In eight of the cases the last sigmoid artery and its proximal anastomosis were very small, and in two cases the artery was not even present. The examples of carefully injected specimens in the articles of Pope and Buie,[105] and Pope and Judd confirm the variation in position and number of vessels in this region.

Thus, a review of the anatomy of the region of the rectosigmoid forces on us a realization of its variability, both in the bowel itself and in its attendant supply of blood. W. J. Mayo,[106] in an anatomic consideration of this region, showed that in 80 per cent of a series of specimens examined, there was distinct narrowing and longitudinal mucosal folds in the terminal part of the sigmoid. This he termed the rectosigmoid. A relationship of the length of this narrowed portion of the bowel and the distribution of the arteries to it, seems probable, but has not been demonstrated.

The vessels of this region have been studied by methods of injection. Because of extensive experience in this type of work, we deem it advisable to place certain limitations on the results of the method. Jamieson and Dobson [107] have expressed similar views. As a means of studying the course, the relationship and anastomosis of vessels and of

103. Manasse, Paul: Die arterielle Gefässversorgung des S. romanum in ihrer Bedeutung für die operative Verlagerung desselben, Arch. f. klin. Chir. 83:999, 1907.

104. Drummond.[88a]

105. Pope, C. E., and Buie, L. A.: A Description of the Arterial Blood Supply of the Pelvic Colon, Tr. Am. Proct. Soc., 1929, p. 78.

106. Mayo, W. J.: A Study of the Rectosigmoid, Surg., Gynec. & Obst. 25:616 (Dec.) 1917.

107. Jamieson, J. K., and Dobson, J. F.: The Lymphatics of the Colon, Proc. Roy. Soc. Med. (Surg. Sect.) 2:149, 1909.

preserving a permanent record of the specimen, the various methods of injecting the arteries are satisfactory. However, it is impossible as well as dangerous to draw conclusions regarding the vascular potentialities of these same vessels during life. The methods have many variable factors. The postmortem contraction of smooth muscle is neither understood nor governable; the extent of the postmortem clotting and the degree of thoroughness with which the vessels are cleansed by different investigators will alter the results, and finally the type of material used for injection and the amount of pressure maintained within the system will alter the extent and valuable qualities of the anastomosis present. It is obvious that although injection of a mesenteric artery will fill the branches of the entire intestinal tract, the suggestion made by one observer that circulation could be maintained by the inferior mesenteric artery after ligation of the superior mesenteric artery is not warranted. Similarly, the evidence of extensive pelvic anastomosis through small vessels after the injection of the inferior mesenteric artery with mercury does not mean that a rectal stump would be preserved from gangrene after ligation of the superior hemorrhoidal artery, as claimed by another observer.

In any deductions from specimens in which the arteries have been injected, it must be remembered that we are drawing conclusions from arteries which have been completely relaxed and stretched by constant internal pressure usually greatly in excess of normal blood pressure. Thus a sclerosed vessel may be distended until its channel is much larger than normal, the exact reverse of the condition during life. Since many patients who are operated on for disease of the colon and rectum are of advanced age with more or less arteriosclerosis, we believe that attempts to draw inferences concerning the blood supply during life from injected specimens should be made with the greatest conservatism.

THE RECTUM

The rectum is supplied by a variable number of small arteries from the superior hemorrhoidal artery before its division, by the right and left branches of the superior hemorrhoidal artery, by the middle and the inferior hemorrhoidal arteries and by a variable amount from the middle sacral artery.

For many years anatomists have described the arterial supply of the upper part of the rectum as coming only from the right and left branches of the superior hemorrhoidal artery. Quénu,[108] in 1893, described a branch from the superior hemorrhoidal artery above its division coursing upward and anastomosing with the last sigmoid

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108. Quénu, E.: Des artères du rectum et de l'anus chez l'homme et chez la femme, Bull. Soc. anat. de Paris **7**:703 (Dec.) 1893.

artery. Later Rubesch described rami of the superior hemorrhoidal artery to the bowel which are given off above the bifurcation and which do not anastomose. Drummond [45] noticed one or two encircling branches, with little anastomosis above or below, given off from the superior hemorrhoidal below the last sigmoid artery. Pope and Buie demonstrated that these vessels are constantly present in varying numbers and that they have some anastomosis with the adjacent arteries. These small vessels supply the bowel in the gap between the termination of the marginal artery in the lower portion of the sigmoid and the division of the superior hemorrhoidal artery (fig. 15). Their course is at once encircling toward the anterior aspect of the bowel and downward, coursing more or less parallel with the longitudinal axis of the rectum on its lateral and anterior aspect. The vessels vary in number from one to five and both number and size are proportional to the anatomic variations encountered in this region, that is, a high, small or absent last sigmoid artery, or a low dividing superior hemorrhoidal artery. They are to be regarded as supplemental and irregular vessels.

The superior hemorrhoidal artery divides near the upper end of the rectum into two branches, a right and a left superior artery (fig. 16). The point of bifurcation is not constant but usually is opposite the second or third sacral vertebra and, in many instances, is marked by absence of the mesosigmoid. Pope and Judd found that the point of bifurcation is 18 cm. from the origin of the inferior mesenteric artery. The branches course downward along the rectum, gradually encircling it from the posterior aspect. The two branches are seldom equal in size. Quénu,[108] in a meticulous study of the arteries in thirteen specimens, found that the right branch is usually the larger, and frequently furnishes a large branch to the posterior surface of the rectum. Branches of the arteries are given off irregularly to pierce the thick musculature of the rectum at an acute angle and ramify in the submucosa. Among the lowest branches are some which anastomose with the middle hemorrhoidal and prostatic or vaginal arteries.

The middle hemorrhoidal arteries are the first vessels to the large bowel to be derived from outside the splanchnic circulation. Their origin is variable, coming either directly from the anterior division of the internal iliac artery, or from a common trunk with the middle vesical, vaginal, prostatic or internal pudic artery. The arteries course forward to the lateral aspect of the rectum along which they descend, sending into it small irregular branches, some of which anastomose with the branches of the superior hemorrhoidal and some with the vaginal, vesicle or prostatic arteries. The middle hemorrhoidal vessels are inconstant in size, distribution and anastomosis. Particular interest has been centered on the anastomosis of the middle with the superior hemorrhoidal artery. Drummond [104] encountered a case in which there

were no middle hemorrhoidal arteries, and Quénu [108] in his more detailed study found the anastomosis extremely irregular. In the thirteen cases examined by Quénu, [108] there was complete failure of anastomosis between the middle and superior hemorrhoidal arteries in one case, the anastomosis was through one side only (most frequently the left) in eleven cases, and was bilateral only once.

It must be concluded, therefore, that although the middle hemorrhoidal artery usually anastomoses with the superior hemorrhoidal
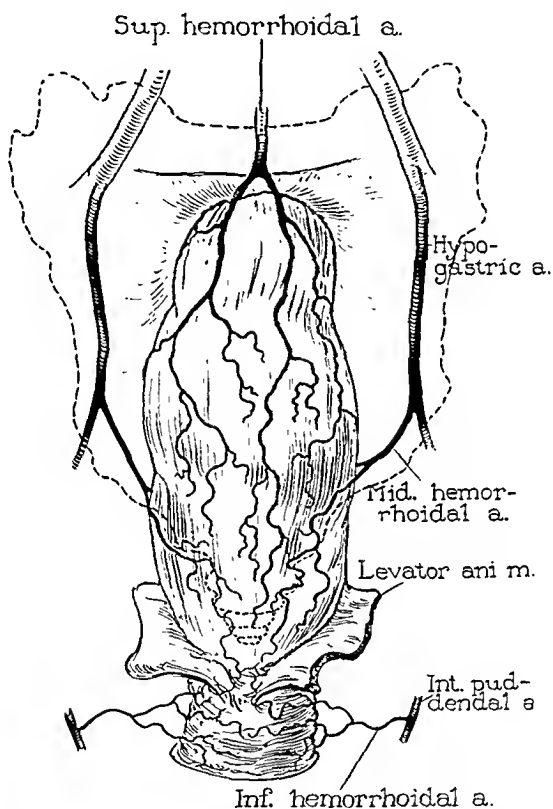
Fig. 16.—Arteries to the rectum (posterior view).

artery as well as with the vesical and prostatic or vaginal vessels, the relationship is not constant and no great reliance can be placed on it surgically.

The last artery to the large bowel is the inferior hemorrhoidal. These arteries, usually one on each side, arise from the internal pudic artery during its course through Alcock's canal in the perineum. The vessels subdivide irregularly into three or four smaller branches which circle the anus anteriorly and posteriorly. The vessels supply the musculature of the anus and by fine twigs anastomose with the middle hemorrhoidal artery.

In specimens of the rectum in which the arteries are carefully injected, an anastomosis with the middle sacral artery is seen. This small vessel originates at the bifurcation of the aorta and descends along the anterior surface of the sacrum. Quénu [108] particularly has noted this vessel, and found that it furnishes two or three small branches directly to the posterior wall of the rectum. Pope and Buie included it in the retrorectal plexus. The artery is small, its branches are inconstant and its value as a supply to the rectum is negligible.

The veins of the rectum have received considerable attention from anatomists because of the anastomosis between the portal and caval systems. The rectal veins correspond in name, number and general course to the arteries. The inferior hemorrhoidal veins drain the region of the anus and sphincter and communicate not only with the middle hemorrhoidal veins above, but also with the veins of the perineum and scrotum. The blood is gathered into several large branches from a perineal plexus, and these branches usually unite before emptying into the internal pudic vein in Alcock's canal.

The middle hemorrhoidal veins are the most important in anastomosing the caval and portal venous systems. Through their connections they communicate both submucosally and perimuscularly with the inferior hemorrhoidal vein, drain the region of the rectum immediately above the internal sphincter and have free submucosal anastomosis with the superior hemorrhoidal vein. Their branches also anastomose freely with the prostatic or vaginal plexus and in some cases the middle hemorrhoidal vein becomes one of the principal veins to return blood from the urinary vesicle. From many ramifications the veins gather into larger branches on each side of the rectum, and, following the course of the middle hemorrhoidal artery upward, the final single trunks join the internal iliac veins.

The largest of the rectal veins are the superior hemorrhoidal. From as low in the rectum as the columns of Morgagni, the blood is collected by a large mucosal and submucosal plexus and returned upward in the submucosa. In this course the vessels unite to form larger twigs which eventually penetrate the thick muscularis of the rectum at an angle and then continue upward parallel to it. As higher branches from the mucosa penetrate the muscle they join the original veins which also receive branches from the perirectal tissues. Near the upper end of the rectum, large right and left veins are formed which accompany the corresponding branches of the superior hemorrhoidal artery. The veins receive small vessels from the region of the rectosigmoid and pelvic colon, and the vessel continues upward to the left of the median line, becoming the inferior mesenteric vein at the level of the left common iliac artery.

One of the early investigators of the veins of the rectum was Duret.[109] For practical purposes he divided the veins of the rectum into an external system, which drained downward into the perineum and internal pudic vein, and an internal system, which drained upward. The external system is anatomically the inferior hemorrhoidal vein with additions that it may receive from the middle hemorrhoidal vein. The internal system is composed of the middle, and principally, the superior hemorrhoidal veins. This division is still adhered to by surgeons, and the connection between the two and thus between the caval and portal systems has been in some dispute.

Duret found that he was able to inject material from the inferior mesenteric vein not only into the external hemorrhoidal system but into the saphenous, femoral and genital veins. Similarly, the superior hemorrhoidal vein could be injected from the internal iliac vein. Quénu,[110] in general, substantiated this study but believed that because of varying results there might be some form of valve between the two systems. Gay[111] maintained the independence of the two systems and has been upheld in his views by Cripps. Cripps thinks there is little connection between the veins of the two systems and that when there is, the flow is always toward the iliac veins. Tuttle has demonstrated the connection between the two systems and emphasized the difficulty of injecting the anastomosis of the two through the sphincter, which he compares to a watershed.

We would like to emphasize a fact here that seems to have been neglected. The middle hemorrhoidal vein is the largest medium of intercommunication between the portal and caval systems. Since the distribution and anastomosis of the middle hemorrhoidal artery are extremely variable, a similar variability may be expected in the middle hemorrhoidal vein, and the extent of anastomosis effected by the rectal vessels between the caval and portal systems will vary in each case.

SURGICAL CONSIDERATIONS

The mortality from operations on the colon has not only been reduced by modern study and technic, but operation is being attempted in more advanced cases, a fact which makes comparisons difficult. A large percentage of operations on the large bowel are performed because of malignant conditions, and the opinion as to the operability of a lesion varies with the surgeon. Therefore, a cautious operator may present

109. Duret: Recherches sur la pathogénie des hémorrhoïdes, Arch. gén. de méd. **144**:641 (Dec.) 1879.

110. Quénu, E.: Études sur les veines du rectum et de l'anus, Bull. Soc. anat. de Paris **6**:601 (July) 1892.

111. Gay, John: On Haemorrhoidal Disorder, London, J. & A. Churchill, 1882 p. 69.

low mortality percentages, as a result of having condemned as inoperable cases in which cure or palliation might have been secured by accepting greater risk. Thus the difficulty of knowing what a writer considers an operable lesion enters into the evaluation of statistics. Undoubtedly the last few decades have seen a widening in the field of operability and an increase in radical surgical procedures on the colon.

The primary purpose of the study of the blood supply of the large intestine was to apply it practically to surgery. Operations on this part of the intestinal tract are fraught with the danger of sepsis, even when most carefully performed, because of the type of bowel and nature of its contents, and the added peril of gangrene in the wall of the bowel from ischemia has undoubtedly been a contributing factor to the hospital death rate. With this thought in mind, an attempt has been made to apply the anatomic facts relating to the blood vessels to the operations usually performed on the large bowel. A description of the technic of the operation aside from its application to the blood supply has been purposely avoided. Some of these procedures have been described by previous writers, as few surgeons have written about the colon without giving some warning as to its circulation.

The colon and its blood vessels are roughly similar to a rubber-tired wheel with few, irregularly placed spokes. The spokes represent the named colic arteries, and the rim represents the marginal artery from which the colon is supplied by the terminal branches. It is important in handling the blood supply of the colon to keep in mind that the arterial pattern of each colon is original. The present study has established a few facts such as the continuity of the marginal vessel and the percentage of occurrence of the various named arteries, but the outstanding fact emphasized is the variability of the arterial pattern, making it essential to deal with each case as a variant. The fact that single colic arteries may be ligated experimentally or by mishap during an operation, and the supply to the bowel maintained by the marginal artery should not be an excuse for carelessness. These arteries should be ligated purposefully and only when occasion demands. The arteries of the colon are variable in size and position, and the two adjacent vessels should be investigated before one artery is occluded. The importance of this cannot be more emphatically proved than by reference to the celloidin cast shown in figure 5. Here ligation of the inferior mesenteric artery would inevitably result in ischemia and gangrene of more than half of the colon. The vessels to the portion of the bowel involved should be identified in all surgical procedures. Identification may be difficult in the presence of excessive fat or adhesions; however, a knowledge of the approximate situation of the vessels and palpation for their pulsations will usually establish their situation.

Mobility.—Mobility of the colon is a decided advantage in dealing with the blood supply. If the part of the bowel involved can be lifted

so that the mesocolon is vertical to the posterior wall, the blood vessels are easily identified even in the presence of moderate obesity. There is nearly always mobility in the transverse portion of the colon, and although we have found a mesocolon to be present in the ascending and
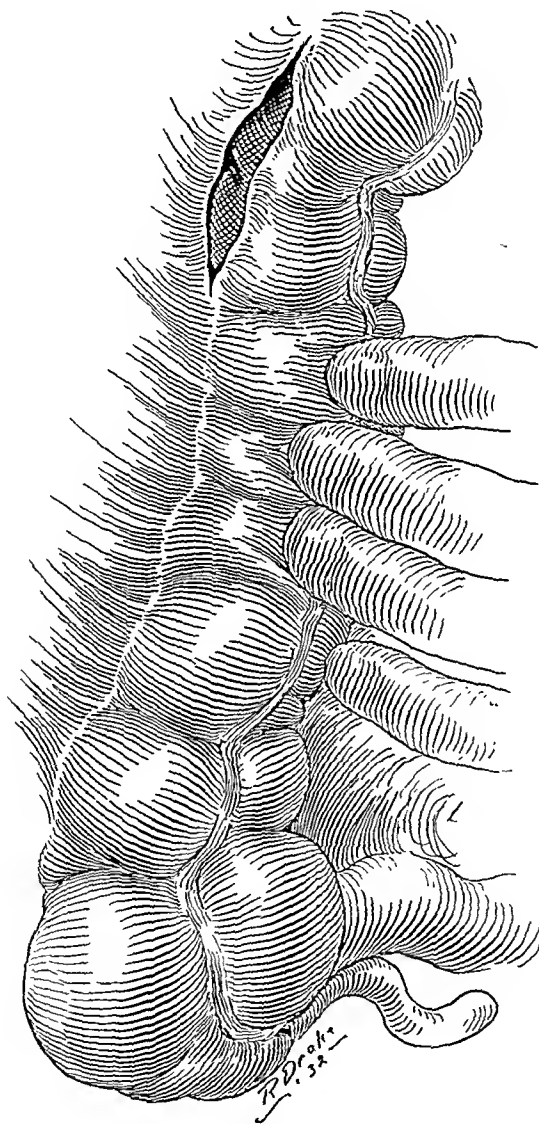
Fig. 17.—Incision along the line of the peritoneal reflection lateral to the colon to obtain mobility.

descending portions of the colon more frequently than Treves' classic figures indicate, it is usually too short to allow any appreciable upward manipulation. To obtain mobility, the peritoneum should be incised along the lateral side of the colon. There is usually slight thickening of the peritoneum at the line where the upward reflection from the

posterior wall takes place, and the resulting white streak may be incised throughout its entire length without danger of encountering vessels (fig. 17). The bowel may then be lifted mesially and upward and the centrally situated blood supply brought into prominent relief (fig. 18).

Insufficient mobilization of the colon, in the course of a procedure in which the bowel is to be fixed, may have several detrimental effects on the blood vessels. Undue pull on the colon will tend to stretch the

Fig. 18.—Colon elevated after incision of the peritoneum along line of its lateral reflection.

vessels to that part longitudinally and thereby decrease the diameter of their lumen. This is particularly true of the marginal and the terminal vessels. Another danger is that acute angulation of more distantly attached vessels may occur, especially at the points where the colon is permanently fixed by ligaments. The blood vessels of the colon lie beneath a loose peritoneal covering which allows considerable movement, and their attachments are only through their inosculations and terminal branches. For this reason, angulation of a vessel several centimeters distant may be caused by tension on the colon, thereby

reducing the anastomotic supply at a point where it is most necessary. This trouble is particularly likely to be encountered in operations in which the bowel is fixed to the wall of the abdomen, such as colostomy, and will be referred to again when these procedures are considered.

The Wall of the Colon.—In the study of the terminal vessels to the colon, we have stressed several important facts: (1) the comparatively scanty anastomosis between the small terminal arteries; (2) the greater vascular supply to the mesocolic two thirds of the bowel, and (3) the subserosal position of the long arteries before they pass beneath the two amesocolic taenia to supply the relatively avascular third portion of the colon. These anatomic peculiarities give us several guides in surgical procedures on the wall of the bowel. The slight anastomosis of the
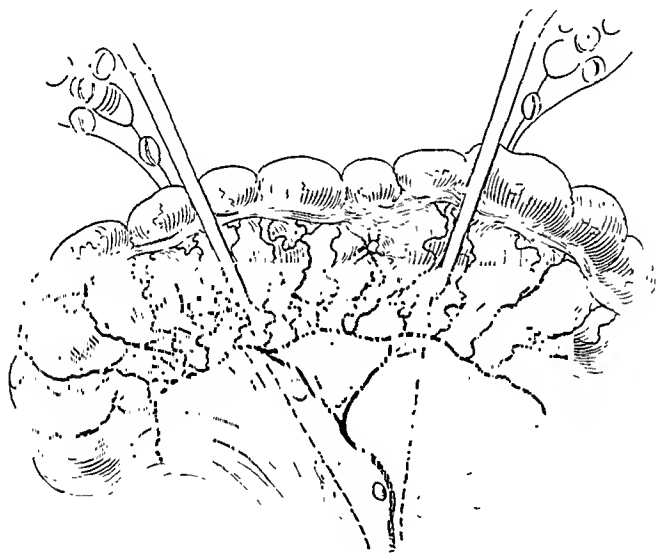
Fig. 19.—Colon cut across at angle to preserve the mesocolic, vascular portion.

arteries demands greater care in handling the large intestine than the small. When the bowel is to be cut across, as for end-to-end anastomosis, a greater part of the vascular mesocolic portion of the colon should be retained than of the amesocolic third. This is accomplished by cutting the bowel at an angle (fig. 19). If the colon is cut perpendicular to its axis, the incision may just include one of the long terminal branches to the amesocolic portion, thus destroying for perhaps 2.5 cm. the only supply to a naturally impoverished portion of the bowel. Pauchet,[112] *without considering the course of the vessels,* advocated cutting the colon at an angle of 45 degrees. So great an angle might make it difficult to obtain sufficient mobilization to avoid

112. Pauchet, Victor: Practical Surgery Illustrated, London. Ernest Benn, Ltd., 1925.

pull on the amesocolic part of the anastomosis in cases in which the colon was large and would result in a sharp angle in the lumen. A more rational rule would be to cut the bowel at less acute angles, so that the two ends will most closely coincide in diameter. Cutting the colon at an angle has the added advantage of producing a larger opening at the anastomosis.

When a longitudinal incision in the colon is necessary, it should be placed in the center of the amesocolic third of the bowel (fig. 20). The closer a longitudinal incision is made to the mesocolic taenia, the greater will be the area of colon between the incision and the outer point on the circumference of the bowel to be furnished by the feeble anastomosis of the encircling arteries of the opposite side and the adjacent terminal vessels. The direct supply to the area will have been sacrificed, and the danger of gangrene will be commensurate with
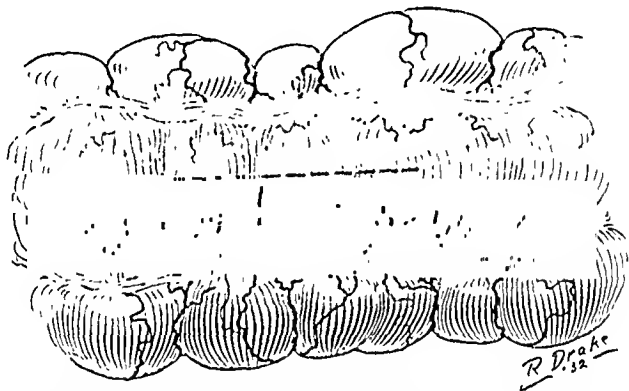
Fig. 20.—The dotted line indicates the site of ligating the marginal artery and resecting the main artery when necessary.

the length of the incision. Fortunately for patients and surgeons, the amesocolic section of the colon is usually the most accessible and the least encumbered with fat, and therefore is the place usually selected for ileocolostomy and insertion of enterostomy tubes. If the anatomy of the terminal vessels to the colon is kept in mind, the surgeon will make only longitudinal incisions in the colon parallel with, and exactly between, the amesocolic longitudinal bands.

The subserosal course of the long terminal arteries exposes them to considerable danger when an effort is made to clear fat away from the colon. These arteries furnish branches to the epiploic appendages before passing beneath the longitudinal muscles to the amesocolic section of the wall. In elevating and clamping fat tabs, it is easy to include the long artery, especially if the colon is contracted, and there is increased redundancy of the arteries. Since these arteries are the sole supply to the outer third of the colon, their value cannot be over-

estimated. As an experiment, the long arteries have been intentionally included when cutting off the epiploic appendages of colostomy loops which are later to be trimmed off and remain as permanent colonic stomas. Usually, although not invariably, there results an area of necrosis in the wall of the bowel near the median line between the taenia. In one case in which the long arteries were ligated on opposite sides of the colon at the same point, necrosis of the wall between the longitudinal bands occurred for about 2.5 cm., the opening, which appeared on the fifth day, being circular. Although there may have been slight impairment of the circulation to the colostomy loop, the resulting necrosis can be regarded only as evidence of the avascularity of this part of the colon and emphasizes the advantage of leaving the
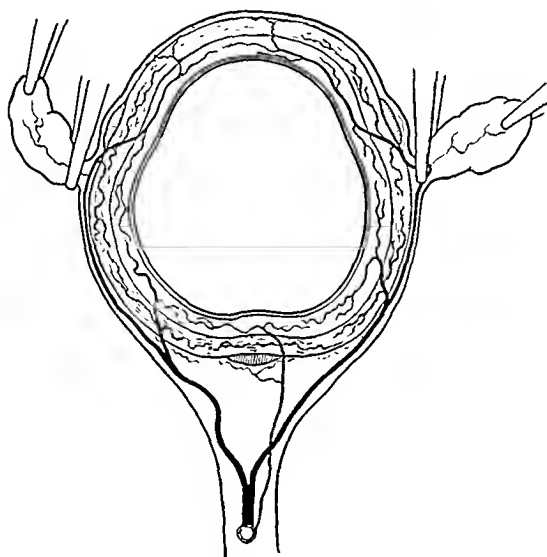
Fig. 21.—The correct (left) and incorrect (right) method of clamping epiploic appendages.

long terminal vessels intact. To avoid injury to the blood supply, the epiploic appendages should not be pulled outward too vigorously, and the clamp should be placed on the neck of the tab, parallel to a tangent at the longitudinal muscle band. (fig. 21). The mesocolic fat should be removed by blunt dissection.

The Marginal Artery.—This artery has been found to be a continuous vessel present in all colons. In a small number of ascending colons (5 per cent), it is replaced by profuse single branches. The distance of the artery from the wall of the bowel varies from a half to several centimeters, and the presence of secondary loops is uncertain. In position and function, the marginal artery is comparable to the water main in a city street. Whenever possible, the artery should be left intact. However, its presence assures the colon of a distal as well

as proximal blood supply, and whenever the occasion demands, the surgeon should have no hesitancy in resecting the marginal artery of the part of the intestine being removed. In fact, it may be desirable in cases of malignant conditions when it is recalled that the second set of lymph nodes, the paracolic nodes, follows its arcades down to the main arteries. When the marginal artery is resected, care should be taken that the remaining artery extends beyond the cut edge of the colon which it supplies (fig. 19). The principle of the wedge or fan-shaped resection applies to resection of the mesocolon with its blood vessels quite as much as to that of the mesentery of the small bowel. Should the wedge of mesocolon include one of the main colic arteries, the artery itself should be made the apex of the resected wedge and ligated as close to its source as is compatible with proper peritonealization of the posterior wall. In this way the resection would include the third set of lymph nodes, the intermediate nodes, which follows the course of the colic arteries.

Colostomy.—The oldest operation on the colon is colostomy.[113] Regardless of the type or position of the colostomy, there are a few fundamental rules which should be remembered with regard to the blood vessels. The colon must be sufficiently mobilized to allow the bowel to extend above the skin of the abdomen without undue pull upward on the peritoneal attachments. This may be accomplished by incising along the lateral peritoneal reflection as described. With the colon freed to allow exteriorization of a small loop without undue pull on the underlying arteries, the immediate vessels must be considered. The marginal artery will be found running more or less parallel with the wall of the colon at a distance varying from a half to several centimeters. This vessel should always be left intact when colostomy is performed as it is the immediate source of supply to the colon and the important anastomosis between the arteries of the colon. In the types of colostomy in which it is desirable to make an opening in the mesocolon, either to draw components of the abdominal wall together below the loop or simply to fix the loop in position on a tube or rod, the opening should be made between the colon and the marginal artery (fig. 22). In order to obtain an opening of sufficient size, it may be necessary to ligate several of the terminal vessels, but this is preferable to ligating the marginal artery or making the opening beneath it. Ligation of the vessel may rob the colon proximal to the colostomy of a valuable anastomotic blood supply, whereas an opening below the artery adds to the first danger a second from the embarrassing amount of bleeding produced by the relatively simple process of cutting across the colostomy opening.

113. Reference Handbook of the Medical Sciences, New York, William Wood & Co., 1900, vol. 1, p. 532; 1901, vol. 2, p. 105.

Some surgeons customarily sew the peritoneum to the elevated colon after performing colostomy. Although we believe that sewing into the colon should be avoided whenever possible, we wish to emphasize here only a point regarding the blood supply. In the mesocolic portions of the colon, the vessels lie loosely beneath the serosa and are often covered with fat. In sewing the peritoneum to the wall of the colon, it is easy to injure or ligate several of the long terminal branches.

Mikulicz Operation.—This operation, which is occasionally performed for malignant disease of the colon, is exteriorization of the loop
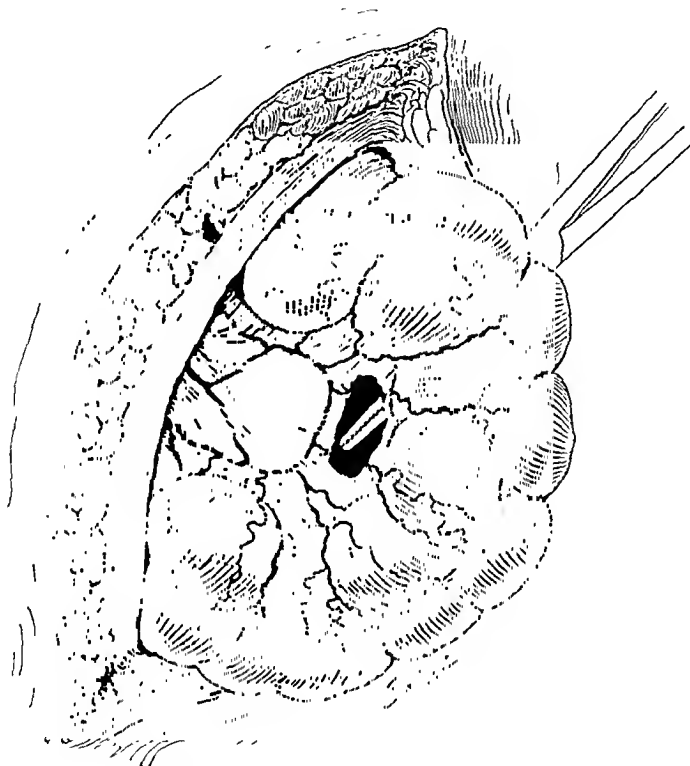
Fig. 22.—Opening between the colon and marginal artery in performing colostomy.

containing the growth, with removal as a second stage of the procedure. It entails several factors into which the blood supply enters. The first consideration is proper mobilization of the part. The procedure is generally reserved for the encircling scirrhous types of malignant growths that make intra-abdominal manipulation hazardous. If this type of lesion is pulled upward under any tension, some circulatory disturbance may result. Since the veins are more easily collapsed than the arteries, passive congestion of the already highly infected mass occurs. The resulting compensatory dilatation and hyperactivity of the lymph channels will carry the infection, if not the malignant growth

itself, downward into the abdominal cavity. To avoid vascular embarrassments, the first consideration in the Mikulicz operation must be sufficient mobilization of the growth and colon to be resected.

Resection.—Resections of parts or all of the colon must be adjusted to the nature of the lesion. There is no advantage in removing the marginal vessel and the main arteries in cases of benign lesions such as polyposis or ulcerative colitis. The handling of the wall of the colon and the marginal artery in resection has been considered, and we wish here merely to advocate primary ligation of the main arteries to the part to be removed. In any case in which an appreciable portion of the colon is to be removed, the operation can be greatly simplified and shortened by ligating the vessels to the part in their central position before an attempt to remove the bowel is made. This necessitates careful identification of vessels and may not be feasible if the patient is obese. For example, in the removal of the right portion of the colon after ileocolostomy has been performed, if the ileocolic, the right colic and the marginal arteries just distal to the anastomosis are ligated first, resection can be made without further clamping and only a negligible amount of blood will be encountered in the distal vessels (fig. 23).

Resection of the splenic flexure frequently offers great difficulty from the technical standpoint. It has been shown that the marginal artery is present in this region, at least before operation, and that there is no lack of blood to the part. However, the splenic flexure lies high, and is deeply placed within the abdomen in the form of a long, inverted U. The blood vessels to the region, through the marginal artery, are almost parallel and close together. If resection of this part is attempted from the median aspect, the marginal arteries are in grave danger of being injured at points proximal to the site of resection. The attack must be lateral to the colon, freeing the splenic flexure along the white line of the peritoneal reflection, severing any connection between the omentum and the spleen and any peritoneal attachments of the colon to the posterior wall. The entire splenic flexure may then be brought mesially and upward with the arteries uninjured, and the resection may proceed as conditions indicate. It would be well to recall that the left part of the transverse colon may have lymphatic drainage upward to the spleen through the thickened left edge of the omentum. For this reason it is advisable to remove this part of the omentum.

Sigmoid.—The sigmoid offers the most favorable site for operations on the large bowel from the standpoint of dealing with blood vessels. The mesosigmoid allows easy exposure of the affected part; the arterial supply is adequate and flexible, due to the secondary loops usually present below the marginal artery, and in addition the sigmoid is low in the abdomen where infection is less dangerous than near the diaphragm. The same rules that apply to handling the blood supply of the colon are applicable in operations on the sigmoid.

Rectosigmoid.—In the region of the lower portion of the sigmoid near the rectum, the form of the blood supply changes. The region has been generally referred to as the rectosigmoid, and from the standpoint of the blood supply, is characterized by lack of the marginal artery, doubtful anastomosis with the arteries of the sigmoid through the small last sigmoid artery, more longitudinal direction along the bowel of the small arteries to the wall and loss of the mesosigmoid in the base of which lies the large superior hemorrhoidal artery. Consider-
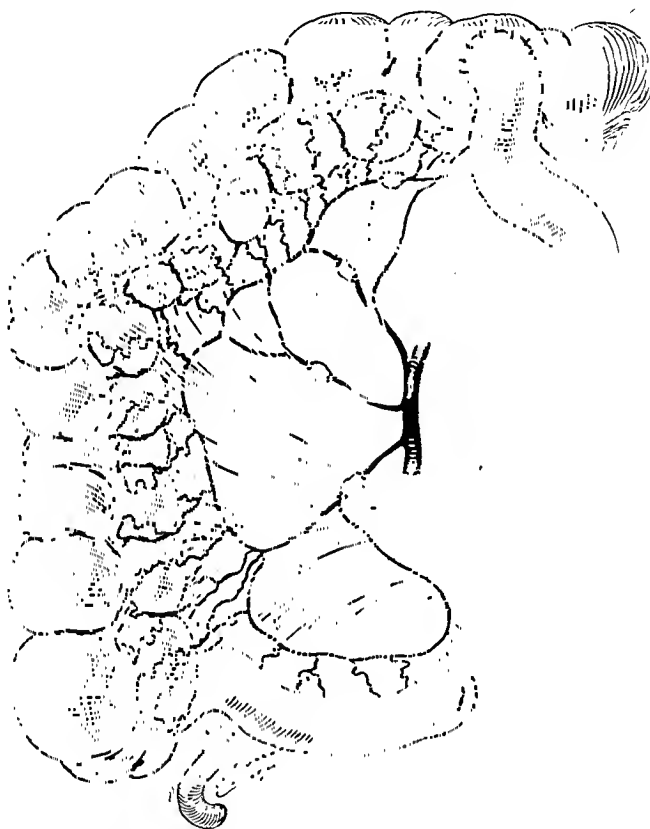
Fig. 23.—Primary ligation of the vessels in removal of the right portion of the colon.

able interest was centered about the part several years ago, when it was customary to pull the sigmoid down and make a posterior artificial anus after resection of the rectum. It was the custom to sever the superior hemorrhoidal artery through an intra-abdominal incision in order to allow sufficient mobility of the sigmoid to bring it down. Sudeck, in studying the vessels of this region, described what was called a critical point for this ligation, just above the last sigmoid artery, which was supposed, through its anastomosing with the marginal artery of the sigmoid, to replace the blood supply to the rectum. If the superior

hemorroidal artery were severed below this point, necrosis of the rectum would result. Later, Drummond [88] studied the region and found that there was no anastomosing artery between the marginal artery and the superior hemorrhoidal artery in 10 per cent of the cases, and that the artery was so small that it was negligible in 40 per cent. The critical point was then moved upward and located just below the first sigmoid artery. However, the sigmoid arteries are extremely variable in their origin and number. They may all rise from the left colic artery or from one large branch of the inferior mesenteric artery. Fortunately, operations making the artificial anus posteriorly have been largely discarded, but the question of blood supply to the rectum is still present in two-stage abdominoperineal resections. Because of variations in the arterial supply in this region, there is but one safe rule to follow: If the superior hemorrhoidal artery is severed, the bowel below that point should be removed at once.

Rectum.—In the rectum, the character of the arterial supply is altered even more noticeably than in the rectosigmoid. The branches of the superior hemorrhoidal artery course downward along the rectum and pass through the thick muscular walls to the submucosa. In the lower part of the rectum, the variable middle hemorrhoidal artery enters to form an anastomosis with the superior hemorrhoidal artery above, and below with the inferior hemorrhoidal artery which supplies the anal canal. Because of the longitudinal direction of the vessels, it is possible to perform posterior resection almost bloodlessly after the lower vessels have been ligated. The superior hemorrhoidal artery is isolated late in the operation on the posterior surface of the rectum or rectosigmoid. There is no danger of ischemia following ligation of this artery, as the bowel below the point is entirely removed. This is likewise true for the less radical local excisions of growths low in the rectum.

The marked variations of the middle hemorrhoidal artery and its frequent rôle as a vesical artery perhaps account for some of the complications encountered in posterior resections of the rectum. The dysuria and retention so marked in some cases following ligation of the hemorrhoidal arteries, may result from having a considerable portion of the supply of blood to the bladder cut off, with consequent increased neurogenic disturbance. Similarly, an occasional vesical fistula following a posterior resection of the rectum may be caused by the ligation of a middle hemorrhoidal artery that was furnishing a large part of the blood to the posterior aspect of the bladder.

CONCLUSION

A thorough study of the blood supply of the large intestine shows conclusively the variability of the arterial patterns, and for this reason the suggestions for surgical procedures are made as general as possible.

EXPERIMENTAL PLEURAL ADHESIONS

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A variety of surgical procedures for abscess of the lung is in practice at the present time, ranging from simple drainage, unroofing and ventilation to pneumonectomy. The most dangerous complication of these operative procedures is entry of the free pleura with resultant fatal putrid empyema. A lung with a putrid focus and a nonadherent, or inadequately adherent, pleura at the site of the focus, therefore, contraindicates operation until adequate adhesions have been formed to prevent pleural invasion. We accept the idea that the pleura partakes in the process of infections of the lung, such as abscess and, sometimes, bronchiectasis. In abscess of the lung the infection is lodged in the smaller bronchi in the early stage of the disease. The lung then undergoes a process of putrid liquefaction, and a more or less extensive surrounding pneumonitis ensues. The adjacent pleura is involved with a resulting pleuritis. As the process extends, the area of pneumonitis enlarges, the pleuritis becomes more extensive and adhesions are formed between the two layers of the pleura. Since the putrid focus is localized in its extent, the pleural involvement, or the pleural adhesions, will be more or less localized over the area of the putrid focus in the lung. Provided exact localization of the abscess has been carefully determined by roentgenographic examination or studies with iodized poppy seed oil 40 per cent, it remains a simple matter for the surgeon to resect a rib or ribs, encounter the pleural adhesions and drain the abscess cavity through them. Nevertheless, even with an abscess exactly localized, the area of pleural adhesions may be too limited or inadequate for a safe procedure. At the edge of the zone of pneumonitis, the pleural adhesions may be weblike in structure. This is especially true in acute abscess of the lung. Any degree of exploration beyond the limited zone of firm adhesions may result in a general pleural infection.

This problem of the surgical treatment of suppurative pulmonary foci is entirely dependent, therefore, on the production of an effective pleural barricade to an infected focus. That this fact is generally recog-

nized is shown by the practice in some clinics of attempting to produce adhesions by suture and by packing with gauze, in order to wall off the putrid focus in the lung prior to operation. The importance of pleural adhesions in operations on abscess of the lung also explains the many attempts at experimental production of pleural adhesions by the intrapleural and the extrapleural routes. Since pleural adhesions could be produced by any one of these methods, it occurred to us (Drs. Hirshfeld and Cohen), while working on the problem of abscess of the lung at Mount Sinai Hospital, to review the available methods from the point of view of efficacy of their production, the simplicity with which they could be formed and the factor or factors underlying their formation.

Intrapleural injections of solutions, such as 50 per cent dextrose, glycerin, gum arabic solutions in varying concentrations, turpentine and corrosive chemicals, were tried and either gave a violent pulmonary reaction in animals or did not inaugurate any pleural reaction whatsoever. It is judged that the intrapleural injection of these substances to produce pleural adhesions is dangerous for clinical trial.

Of the extrapleural methods the application of chemicals was first tried. When chemicals are applied to the endothoracic fascia, either a local abscess or a simple inflammatory process may ensue without giving rise to pleural adhesions. In some cases they may give rise not only to a pleuritis which results in adhesions, but in addition to a rather violent pneumonitis. The procedure associated with the least danger, and the greatest efficacy was found to be extrapleural compression. This was accomplished by packing tightly against the endothoracic fascia beneath a rib. Both gauze and sea sponges were used to produce extrapleural compression. In each case adhesions were produced, showing that the common factor responsible for the production of adhesions in the pleura was the effect of pressure, irrespective of the substance or substances used.

EXPERIMENTS

A limited number of experiments were done to note the effect of application of chemicals to the parietal pleura. A number were also done to note the effect of extrapleural compression by means of gauze or sponges. Microscopic sections were made of specimens showing pleural adhesions. Only typical experiments will be cited, and a few illustrative microscopic sections will be fully described.

Dog 11072.—On Oct. 22, 1931, with the animal under ether anesthesia, two ribs were resected on the left side for about 3 inches (7.6 cm.). Intercostal muscles were removed. Gauze soaked in turpentine in olive oil (1:2) was applied to the parietal pleura. The gauze was left in place for about fifteen minutes and then removed. The dog was killed on October 29. Postmortem examination disclosed no pleural adhesions.

Dog 11114.—On Nov. 12, 1931, with the dog under ether anesthesia, the fifth and sixth ribs on the right side were removed for a distance of about 3 inches. Gauze soaked in oil of eucalyptus was applied to the parietal pleura and was then removed. The same procedure followed on the left side. The dog was killed on November 19. Postmortem examination disclosed that both right and left pleural surfaces were intact and free from adhesions.

Dog 11073.—On Oct. 22, 1931, with the dog under ether anesthesia, two ribs were resected subperiosteally on the left side for a distance of about 3 inches. Two layers of gauze soaked in turpentine in oil (1:2) were packed into the wound extrapleurally. The wound was closed in layers. The dog was killed on October 26. Postmortem examination disclosed a large subcutaneous abscess at the site of application of gauze with the oil. In addition there was a diffuse bronchopneumonia in the underlying lung. The pleurae were free of adhesions.

Dog 11089.—On Oct. 29, 1931, with the dog under ether anesthesia, two ribs were resected subperiosteally on the right side. The parietal pleura was exposed and was then soaked with eucalyptol over an area measuring about 6 inches (15.2 cm.). The wound was closed in layers. The dog was killed on November 5. Postmortem examination disclosed adherent pleura over the area painted with eucalyptol. The right lung was adherent to the pleural surface over an area about 2 by 5 cm. The parietal pleura adjacent to the adhesions was reddened and thickened.

Microscopic Examination.—A section through the thoracic wall and the adherent lung showed that the lung was fixed to the wall of the chest by a delicate granulation tissue well supplied with fibroblasts, capillaries and slender collagen fibers. The adjacent lung showed an interstitial infiltration with phagocytic cells and a dilatation of the interstitial capillaries which extended throughout the entire adherent piece. There did not seem to be any alveolar exudate or any exudate in the bronchi. The parietal and visceral pleurae on either side of the adhesions were covered with a thick fibrinous exudate mixed with many red blood cells and a moderate number of polymorphonuclear leukocytes and mononuclear cells. Beneath this exudate was newly formed granulation tissue. In the thoracic wall all of the tissues were edematous and the inflammatory reaction had separated many of the muscle fibers. In some areas there had been extravasations of red blood cells and a proliferation of fibroblasts. In some areas, also, there were huge numbers of phagocytic cells, some of them of giant proportions. Many of these seemed to contain foreign material which possibly bore some relation to the eucalyptol, although no definite oily droplets were found.

One got the impression that there had been a tremendous inflammatory response to the eucalyptol which had resulted in a fibrinous exudate on the pleural surfaces. This, however, had not been destructive enough to prevent the growth of adhesions between the visceral and parietal pleurae.

Dog 11159.—On Dec. 3, 1931, with the animal under ether anesthesia, two ribs were exposed on the left lateral wall of the chest. Parietal pleura with the periosteum was stripped from both ribs for a distance of 3 inches. Intercostal muscles between the two ribs were excised. A packing of gauze soaked in eucalyptol was placed beneath the ribs extrapleurally so as to get extrapleural compression. The dog was killed on December 10. Postmortem examination disclosed extensive adhesions of pleura over the area where the gauze was placed. Superficial muscles about the area of operation were edematous and red. Adhesions between the pleurae covered an area of about 6 inches and were very firm.

As is seen from the foregoing experiments, the application of chemicals, oil of eucalytus or oil of turpentine to the parietal pleura either fails to produce adhesions or may induce an abscess in the superficial tissues with bronchopneumonia in the underlying lung. In only one experiment in which a great deal of eucalyptol was used was a severe pleuritis with adhesions produced. When chemicals are applied with extrapleural compression, a severe inflammation of the surrounding tissue ensues with the production of adhesions.

Dog 10775.—On Feb. 5, 1931, with the dog under ether anesthesia, a small section of the second rib anteriorally on the right side was removed. The pleura was entered and closed by mattress sutures of the lung of the soft parts. The pleura was stripped down over an area below the rent, and three large pieces of sterile sea sponge were inserted to produce extrapleural compression. The wound was sutured in layers.

The dog died on March 11. Postmortem examination on March 12 disclosed a tension pneumothorax below the wound. The lung was firmly adherent to the wall of the chest where it had been sutured. Sponges showed early organization, and the pleural surfaces were adherent deep to the area of compression.

Dog 10802.—On Oct. 3, 1931, with the dog under ether anesthesia, gauze packing was placed beneath the fourth and fifth ribs after the periosteum was stripped away. Pressure was applied to the underlying pleura and lung by tight packing of gauze. The dog was killed on December 10. Postmortem examination showed the entire lung adherent to the lateral thoracic wall. On the external surface was the opening of a cavity from which most of the gauze packing had been removed. In its depths two ribs were exposed, and both were denuded of periosteum. The deep surface of this cavity was formed apparently by the fusion of parietal and visceral pleurae. They were so fused that they could not be separated. The lung deep to the area of direct pressure represented by the cavity seemed compressed and paler than the rest of the lung, although it was still air-containing. The main bronchial divisions were unaffected insofar as their caliber was concerned.

Outside of the area of direct pressure, organized adhesions joined the parietal and visceral pleurae for a variable distance. Anteroposteriorly, the adhesions covered the entire external surface of the lung. From above downward about half of the external surface of the lung was fixed to the thoracic wall. Adhesions had fixed the interlobar pleural surfaces together.

Microscopic Examination.—A large section had been taken through the lung, a portion of the cavity with the adhesions on either side of it and the lateral thoracic wall. Where the pleurae were adherent to one another, the adhesion was formed by a thick layer of fibrin into which fibroblasts and capillaries had grown from both surfaces but at the place where the section was made had not completely bridged the gap. The cavity itself and all the visceral and parietal pleurae were covered with a fibrinous exudate with many inflammatory cells, into which fibroblasts and capillaries had grown. Some of the interlobar pleurae had complete cross fibrous union. On the lung side of the cavity the visceral and parietal pleurae had been iused and were united by complete fibrous union.

The lung showed many patches where the alveoli were filled either with an acidophilic, finely granular material or with red blood cells. There was little exudate of cells and these were found chiefly in the septums. The bronchi had some exudate in them, chiefly of phagocytic cells. The wall of the chest showed

some fibroblastic proliferation between some of the muscle bundles, some degeneration of individual muscle fibers and a subperiosteal formation of bone on the pleural side of two of the ribs.

Dog 11189.—On Dec. 17, 1931, with the animal under ether anesthesia, the sixth rib was exposed on the left thoracic wall. The periosteum was stripped for a distance of about 3 inches. Two inches (5 cm.) of the rib was resected. Packings of gauze were placed in a circular fashion under both open ends of rib and under adjacent upper and lower ribs.

The dog was killed on December 22. Postmortem examination showed the left pleura adherent in a circular fashion at the points where the gauze was applied.

Fig. 1 (dog 11189).—Fibrous adhesions join the parietal and visceral pleurae beneath the cavity from which the gauze had been removed. The underlying lung was partly air-containing.

After making longitudinal sections paralleling the ribs, a large cavity was found tightly packed with gauze. From above downward this measured 6 cm. The cavity was bounded mesially by what seemed to be fused lung and parietal pleura, while laterally was the wall of the chest. Here the ends of the denuded and partially resected sixth rib projected into the cavity separated by a space 1.3 cm. wide. The whole cavity was lined with a dirty yellowish membrane to which the gauze was not adherent. The adhesions between the lung and the pleura about this cavity varied from 5 to 10 mm. in width. The underlying lung seemed compressed and hemorrhagic, but was air-containing. The entire visceral and parietal pleural surfaces seemed dull and thickened.

Microscopic Examination.—A section had been made through a portion of the cavity where it was about 2.5 cm. wide. The section had been made parallel with the rib and included the lung and wall of the chest. The cavity which contained the gauze was lined with granulation tissue and in places had some fibrinous exudate on its surface. The mesial portion of the cavity showed that the parietal pleura together with an intercostal nerve and vein had been forced inward by the pressure of the gauze (fig. 1). The parietal pleura was united firmly to the visceral pleura by a membrane composed of fibrin, capillaries, fibroblasts and collagen fibers which varied from 0.25 to 1 mm. in width (figs. 2 and 3). As one passed away from the zone of greatest pressure the visceral and parietal pleurae were more widely
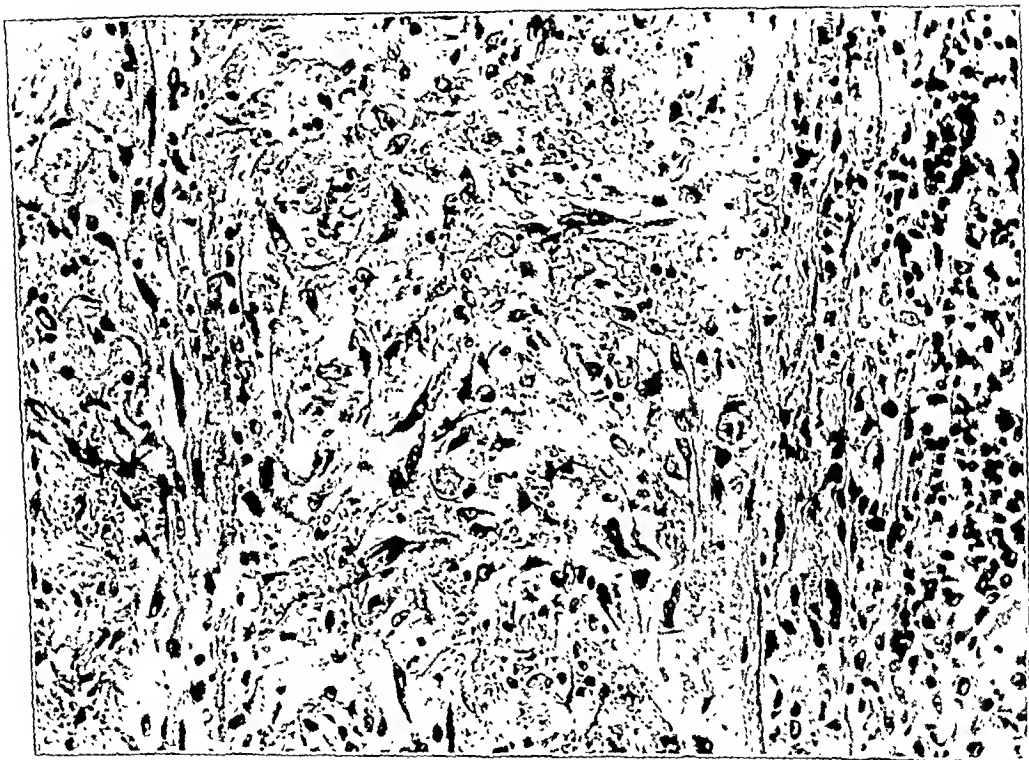
Fig. 2 (dog 11189).—A section stained with Masson's trichome stain. The firm union between the parietal pleura at the left and the visceral pleura at the right is shown. The space between the pleurae is filled with fibroblasts, blood vessels, collagen fibers and remnants of fibrin.

separated and the strong fibrinous adhesions had not been completely organized. The compressed lung showed that many of the alveoli were solidly filled with red blood cells, phagocytic cells containing blood pigment and alveolar cells (fig. 4). In some of the bronchi there were mucin and some cellular exudate. A section of the parietal pleura at a long distance from the region of compression showed that there had been a subpleural proliferation of fibroblasts and capillaries so that even here the pleura was much thickened.

From the foregoing and other unquoted experiments on dogs, it seemed evident to us that with extrapleural compression, either by

gauze or by sea sponges, firm pleural adhesions could regularly be formed. The adhesions joined the pleurae not only in the compressed area but for a variable extent outside of it. We believe that the area of pleural adhesions may be directly related to the degree of compression. By varying the degree of compression the adhesions may be either greater or less in area. We wish to emphasize the time interval at which the fibrous adhesions are formed. In the case of extrapleural compression with gauze, we found them well developed after from five to seven days.

Fig. 3 (dog 11189).—A section stained with Laidlaw's stain. The area is similar to that seen in figure 2, and shows the density and number of the new reticulin (collagen) fibers. The fibroblasts are unstained.

COMMENT

Although pleural adhesions were produced by the extrapleural application of eucalyptol, we believe there are two objections to its use: (1) It is unreliable, and (2) it produces an excessive inflammatory reaction. In our experiments the application of pressure over the pleural surfaces with gauze or sea sponges always resulted in the formation of organized pleural adhesions, usually in from five to seven days without marked associated inflammatory response on the part of the lung. The

primary response in the pleura was a fibrinous exudate which rapidly became organized by fibroblastic tissue. The inflammatory reaction in the lung was minimal, and the bronchial exudate was composed of phagocytic cells.

Of the substances used to produce extrapleural compression gauze offered the best assurance of firm pleural adhesions in the shortest
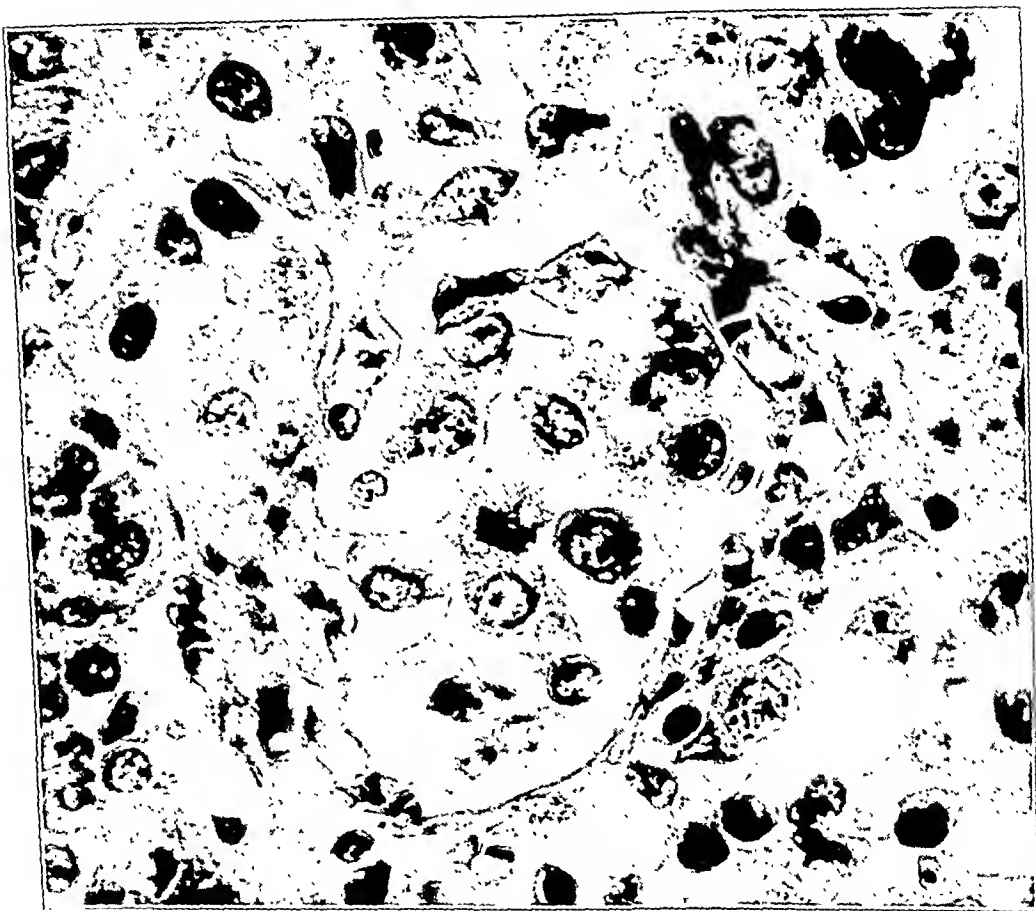
Fig. 4 (dog 11189).—A section showing the alveoli of the lung near the pleural surface filled with alveolar and mononuclear phagocytic cells.

period of time. The degree of compression with gauze could be controlled by varying the number of strips applied under the ribs.

In this paper it has been assumed that if the pleurae are sufficiently compressed to damage their lining cells, they will be joined by organized fibrous adhesions. In this process we believe that the following factors play a rôle: (1) the presence of a foreign body, such as gauze; (2) partial atelectasis of the lung tissue immediately underlying the area of compression; (3) reflex immobility of the lung and pleura as the

thoroughly. The hands of the subject were carefully washed, rinsed and dried. When the skin had regained its normal moisture, the finger tips were placed lightly on the surface of the plate, not more than 2 fingers per plate. Care was taken not to crack the agar, although this occasionally happened. The fingers were left in contact with the agar surface for five minutes. The greatest care was taken that the hands in no way came in contact with any drug, but no effort was made to keep the washed skin free from bacteria. After the imprints were made the plates were incubated for twenty-four hours at 37.5 C., as experience had shown that further incubation did not visibly alter

I.ANTHRAX.HUMAN SKIN, UNTREATED.

Fig. 1.—Agar plate, seeded with ninety day anthrax spores and showing a zone of inhibition on and around a print of normal human skin, left in contact with the inoculated plate for five minutes. Photograph taken after twenty-four hours of incubation at 37.5 C. A transfer, made five days after inoculation from the center of the clear zone, was sterile.

the results. After incubation the plates invariably showed numerous fine colonies of bacteria, evenly distributed throughout the medium, except in cases in which inhibition was observed. In such cases there were sharply outlined zones of inhibition entirely free from any colonies of the test organisms, as shown in figures 1 and 2. These zones extended not only throughout the depth of the agar, but also laterally for varying distances beyond the area of the fingerprints. Transfers

for the sterility of such zones of inhibition were made by cutting out a piece of agar from the center of the zone with a platinum loop and subculturing this agar in broth. Such tests, made with every type of organism used, including anthrax spores, were almost always sterile.

In some cases a heaping up of colonies was seen at the limits of the prints in cases showing no inhibition. In cases of inhibition, this same concentration of growth was frequently observed, not at the edge of the clear area, but slightly beyond it, with a narrow zone of apparently normal growth between this denser ring and the bacteria-free

ANTHRAX SPORES.NORMAL SKIN.
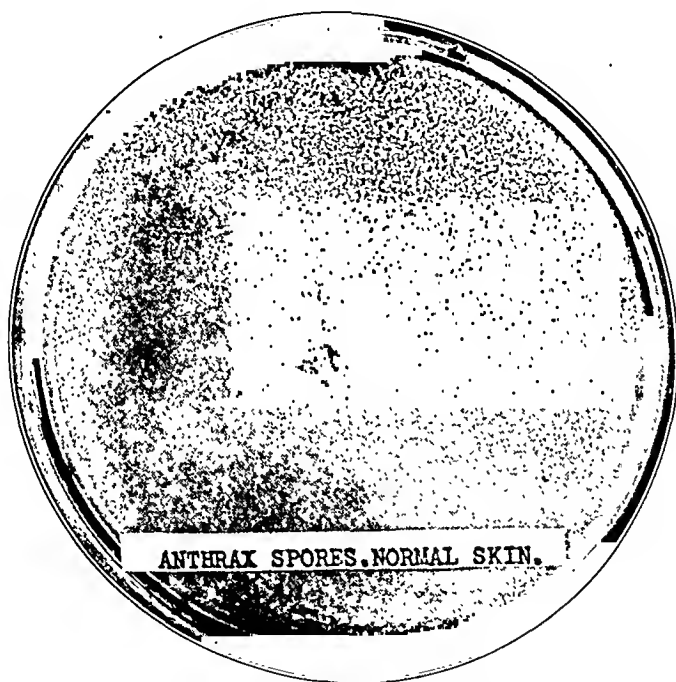
Fig. 2.—Result of an experiment exactly similar to that shown in figure 1, but made on a different date. The zone of inhibition extends only slightly beyond the fingerprint.

area. Overgrowth of other than the test organism was observed on fingerprints on both inhibited and uninhibited plates. These overgrowths of organisms present on the skin, in cases in which inhibition of the test organism was present, indicated in another way the selective action of the skin, which will be described later.

The possible influence of pressure on the growth of the plates was controlled by contacts with glass stoppers and with fingers encased in rubber gloves. Such contacts gave no inhibitions. With the pressure factor relatively the same in all tests, it seems improbable that this had

any significance in the tests in which inhibition was observed. The fact that when inhibition was present it extended below and often laterally far beyond the actual area of contact with the skin would seem to preclude the possibility of some physical or mechanical action attributable merely to the contact of the skin with the agar. Moreover, this factor was the same in all tests, regardless of the observations. Although the hands were carefully rinsed, controls were made with a small amount of soap left on the skin, but no inhibition was obtained.

OBSERVATIONS

All the inhibition tests are summarized in table 1. This table shows that by this method definite inhibition of bacterial growth may occur,

TABLE 1.—*Summary of All Tests of Inhibition of Normal Human Skin*

Organism	Total No. of Tests per Person	Number of Inhibition Zones Found						Total Number of Tests	Total Inhibitions	
		Female			Male				Num- ber	Per Cent
		1	2	3	1	2	3			
Staphylococcus aureus										
Old	30	2	1	8	5	11	4	180	31	17.2
New	30	1	0	2	0	5	2	180	10	5.5
B. prodigiosus	30	0	0	2	2	16	9	180	29	16.1
B. pyocyaneus	30	0	0	1	3	4	0	180	8	4.4
Proteus	30	2	0	0	1	0	0	180	3	1.6
Colon group										
Escherichia no. 3	15	1	0	2	1	6	0	90	10	11.1
Escherichia no. 4	15	7	3	7	1	7	5	90	30	33.3
Aerobacter no. 8	10	0	0	0	0	2	2	60	4	5.5
Aerobacter no. 9	10	0	0	0	0	2	2	60	4	6.6
Aerobacter no. 10	10	0	0	0	3	0	0	60	3	5.0
B. subtilis, spores	30	9	9	12	8	14	11	180	63	34.0
B. anthracis, spores	..	..	..	4	..	..	..	4	4	(100)
Total	240	22 9.1%	13 5.4%	38 15.5%	24 10%	67 27.9%	35 15.4%	1,444	199	13.7

but that such inhibition is far from constant. Thus, in 1,444 tests, inhibition was obtained in 199 instances or 13.7 per cent. Moreover, the action of the skin differed markedly with different organisms, varying, in the comparable series, from inhibition in 34 per cent of the tests with the gram-positive, spore-forming bacillus to inhibition of only 1.6 per cent of the tests with Proteus.

These variations in the action of skin on different organisms offer certain striking exceptions to the usual behavior of lethal agents on bacteria. Thus, with anthrax spores, tests made on four different days showed in all cases an actual killing of these spores, which are notably resistant to other lethal agents. Although the number of tests with anthrax spores was small, these observations were confirmed with the gram-positive, sporulated bacillus, with which more inhibitions were obtained than with any other organism. Inhibition was noted in 63 cases, or 34 per cent of the 180 tests done with this organism, while with all the vegetative forms studied, the incidence of inhibition was

lower. With one exception, a colon group bacillus, Escherichia no. 4, which was inhibited in one third of its tests, there was a striking difference between the spore-forming and the vegetative cells, none of which, with this one exception, was inhibited in more than 17.2 per cent of the tests. The results with skin inhibition, therefore, in regard to spores and vegetative cells, are exactly the opposite of those noted with the usual chemical and physical means of disinfection. The strains used in this study have been carefully tested to be sure that they are not atypical in this respect.

In regard to the vegetative forms, the most resistant was Proteus. Bacillus pyocyaneus paralleled in these tests its known high resistance to chemical disinfection. Within the colon group of bacilli the similarity to chemical disinfection was close. It has been shown by one of us (Hill) that varieties of the genus Escherichia, that is, B. coli and closely related forms, are much more influenced by chemicals than those of the genus Aerobacter, that is, B. lactis-aerogenes and similar organisms. In the present study, the two Escherichia strains tested were inhibited in 40 cases, or 22.2 per cent of the tests. There was, however, a sharp difference between the two strains. With the three Aerobacter strains, the results were uniform, but the incidence of inhibition, 6 per cent, was much lower than in the case of Escherichia strains. Marked difference between the two strains of Staphylococcus aureus was noted, as the old strain was inhibited in 31 cases, or 17.2 per cent of the tests, while the strain freshly isolated from a furuncle was inhibited only 10 times, or in 5.5 per cent of the tests. It would be interesting to determine the relation, if any, between the incidence of inhibition and the virulence of an organism.

In regard to the variations of different individuals, there were 240 comparable tests made by each of the 6 subjects. The maximum incidence of inhibition for an individual was 27.9 per cent; the minimum, 5.4 per cent. The women inhibited in 15.5, 9.1 and 5.4 per cent of their tests; the men in 27.9, 15.5 and 14.5 per cent. The total number of cases of inhibition, therefore, was 69, or 9 per cent of the 720 tests made by women, and 123, or 17 per cent of the same number made by men.

Tests were made with the 10 fingers of a subject on the same day to determine possible differences in them. The results are summarized in table 2. These figures represent the maximum width and length of the zones of inhibition. It is probable that there is a mathematical relation between the area of the print, the number of organisms and the amount of inhibition, but until we have some method of measuring the variable amounts of inhibitory substance present, this cannot be determined.

In view of Fleming's [4] work on the bacteriolytic element or lysozyme which he was able to demonstrate in many different tissues, we performed a number of tests to demonstrate any possible lytic action of normal human skin. Fleming, working with Micrococcus lysodeikticus, an organism particularly susceptible to lysis, reported that a 1 : 100 skin extract gave an incomplete lysis of the test organism in one hour, a small degree of lysis as compared with the action of tears, nasal mucus and some other substances tested. Fleming and Allison [5] believe that the difference is not due to a different lysozyme in different tissues but to quantitative variations. We tried a few experiments by Fleming's method, i. e., putting a thin layer of agar over a plate that had been inoculated the day before, and making fingerprints on top of the second

TABLE 2.—*Diameters of Zones of Inhibition*

	Right Hand, Cm.	Left Hand, Cm.
Thumb	3.2 × 3.6	3.3 × 4.4
Forefinger	3.0 × 3.1	2.9 × 3.0
Middle finger	3.0 × 3.1	3.2 × 3.5
Fourth finger	3.3 × 3.4	2.8 × 3.2
Little finger	3.2 × 3.3	3.3 × 3.6

TABLE 3.—*The Bacteriolytic Action of Normal Human Skin*

Organism	Total Number of Tests	Complete Lysis	Partial Lysis	No Lysis
Gram-positive spore former (B. subtilis)	23	1	2	20
Staphylococcus aureus (2 strains)	24	1	0	23
B. prodigiosus	48	1	4	43
Escherichia	6	0	0	6
Aerobacter	2	0	0	2
	103	2 1.9%	6 5.8%	94

layer. After the second incubation of such plates, readings were difficult when the skin inhibited growth in the top layer, without lysing colonies in the lower layer. We therefore preferred to make fingerprints directly on incubated plates, as this in no way altered the appearance of the plates except when lysis occurred. Our experiments on lysis are reported in table 3.

It is seen from table 3 that the presence of a lytic substance in the skin was rare. In 103 tests, with 5 organisms, complete lysis was obtained only three times, twice with the spore-forming bacillus and once

4. Fleming, A.: Proc. Roy. Soc., London, s. B, **93**:306, 1922. Fleming, A., and Allison, V. D.: Brit. J. Exper. Path. **3**:252, 1922. Fleming, A.: Lancet **2**:217 (Feb. 2) 1929.

5. Fleming, A., and Allison, V. D.: Proc. Roy. Soc., London, s. B, **94**:142, 1922-1923.

with B. prodigiosus (fig. 3). There were 6 cases of partial lysis, in which there was a definite diminution of the number of colonies, but without complete disappearance of the growth. Fleming and Allison [5] believe that lysis due to the action of a lysozyme is not attributable to a phage. It is interesting to note that the skin may on a given day kill the bacteria present in an unincubated plate, but at the same time be unable to dissolve colonies of the same organism. Whether the skin has at least two types of action on bacteria or the difference is only quantitative can only be conjectured at this time.

No evidence was obtained of any variations during the two menstrual cycles covered by these experiments, although Fisher [6] has made some

Fig. 3.—Bacteriolysis. The plate had been seeded with B. subtilis spores, incubated for eighteen hours, after which the entire plate showed heavy growth. The fingertip was left in contact with the surface of the culture for five minutes, and the plate was again incubated for eighteen hours, after which a perfectly clear zone was found, extending slightly beyond the print and through the depth of the medium.

observations in regard to this aspect of the problem. It seems that a much larger series would have to be studied before definite conclusions could be drawn. If an increase of inhibitive action was shown during menstruation, the observation might well be correlated with the work of Macht and Lubin [7] on the menotoxin.

6. Fisher, V.: Proc. Soc. Exper. Biol. & Med. **28**:952, 1931.

7. Macht, D. I., and Lubin, D.: J. Pharmacol. & Exper. Therap. **22**:413, 1924.

sia, below the values taken as normal and then a gradual increase on further etherization. Mahler [7] found that in man ether anesthesia produced a continuous rise in blood cholesterol proportional to the duration of the anesthesia. His longest period of anesthesia was one hundred minutes. He found no rise under nitrous oxide-oxygen anesthesia. Lattes [8] found no rise from chloroform anesthesia. Manceau [9] reported a slight rise in the blood cholesterol of monkeys from both chloroform and nitrous oxide anesthesia. Ginesty [10] found the blood cholesterol lower after barbital anesthesia than it was beforehand. However, no determinations were made during narcosis. Recently, Gray [11] reported a definite rise in blood cholesterol after three weeks of repeated administrations of chloroform.

TECHNIC

Both dogs and rabbits were used in the experiments. Avoiding excitement as much as possible, the dogs were tied on their backs to an operating table. The femoral vein was exposed under 2 per cent procaine hydrochloride anesthesia. The dogs were kept quiet by petting and if excited were quieted for from twenty to forty minutes before the experiment proceeded. Approximately 1 cc. of blood was drawn from the exposed vein, twice in succession, and both samples were run in duplicate as normal blood cholesterol values. Ether anesthesia was instituted by the use of the ordinary closed dog mask attached to an ether bottle. The amount of ether given was kept constant, varying only with each dog initially, and in most instances producing complete relaxation without loss of the corneal reflex. One cubic centimeter of blood was drawn at intervals varying from every few minutes to every half hour. All samples were run in duplicate. The ether experiments in dogs covered periods of anesthesia up to ten hours. Rabbits were treated in the same manner except that they were placed in ordinary rabbit boxes and blood was drawn from the ear vein without local anesthesia. The ether was administered through a similar smaller apparatus. Anesthesia was continued for from four to six hours. Sackett's modification [12] of Bloor's method was used for the determination of the blood cholesterol values. This method requires but 0.25 cc. for each determination, so that the amounts of blood used eliminated any great hemorrhage factor. The total cholesterol of the whole blood was determined. In the experiments

7. Mahler, A.: J. Biol. Chem. **69**:653, 1926.
8. Lattes, L.: Arch. f. exper. Path. u. Pharmakol. **66**:132, 1911.
9. Manceau, P.: Compt. rend. Soc. de biol. **92**:1507, 1925.
10. Ginesty, Lassalle and Mériel: Compt. rend. Soc. de biol. **91**:1399, 1924.
11. Gray, S. H.: J. Biol. Chem. **87**:591, 1930.
12. Sackett, G. E.: J. Biol. Chem. **64**:203, 1925.

in which the blood sugar was measured also, an extra cubic centimenter of blood was drawn each time for the sugar determinations. Byrd's [13] modification of the Folin method for the determination of blood sugar was employed, with the additional modification that 1 cc. of blood was used instead of 0.1 cc., and other solutions in corresponding amounts.

Experiments with chloroform were conducted in a similar manner, this anesthetic being substituted for ether in the ether bottle. Animals were anesthetized for as long as ten hours. Similar experiments were performed under nitrous oxide and ethylene anesthesia, using an apparatus to which was attached an ordinary dog mask containing an expiratory valve. Anesthesia was continued for from four to six hours with ethylene, and up to nine hours with nitrous oxide.

DATA

1. *Blood Cholesterol.*—Ether Anesthesia in Rabbits: The experiment was performed on six rabbits. The blood cholesterol values taken as normal varied from 60 to 96 mg. per hundred cubic centimeters of blood. Blood was drawn every fifteen or thirty minutes after the initiation of ether anesthesia. The changes in blood cholesterol values are shown in chart 1, on which is represented the amount of change from the normal value for each rabbit. The results of three typical experiments are charted, together with an average curve of the changes in all six rabbits averaged for each time period. It will be noted that the blood cholesterol began to rise rapidly with the advent of anesthesia and continued to do so for from forty-five to sixty minutes. Continued anesthesia was not accompanied by a further rise, but the hypercholesteremia began to decrease somewhat less rapidly than it rose, and then more slowly continued to drop toward normal, reaching it after about four hours of anesthesia. The peak of hypercholesteremia, then, is seen to occur after approximately one hour of anesthesia, the amount varying from 38 to 100 mg. above the normal.

Ether Anesthesia in Dogs: Ten dogs were used. The values taken as normal ranged between 130 and 150 mg. per hundred cubic centimeters of blood. In five dogs ether anesthesia was slowly induced to such a degree as to produce complete relaxation but not to such an extent as to abolish the corneal reflex (surgical anesthesia). The amount of ether given was then kept constant. Blood was drawn as before. Three typical examples of the blood cholesterol changes are illustrated on chart 2a; the values represent the changes from the normal as determined for each dog. The blood cholesterol was found to fluctuate more than in rabbits, but a similar change is seen. A peak in the hypercholesteremia occurs after from thirty to ninety minutes

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13. Byrd, T. L.: J. Lab. & Clin. Med. **2**:67, 1925.
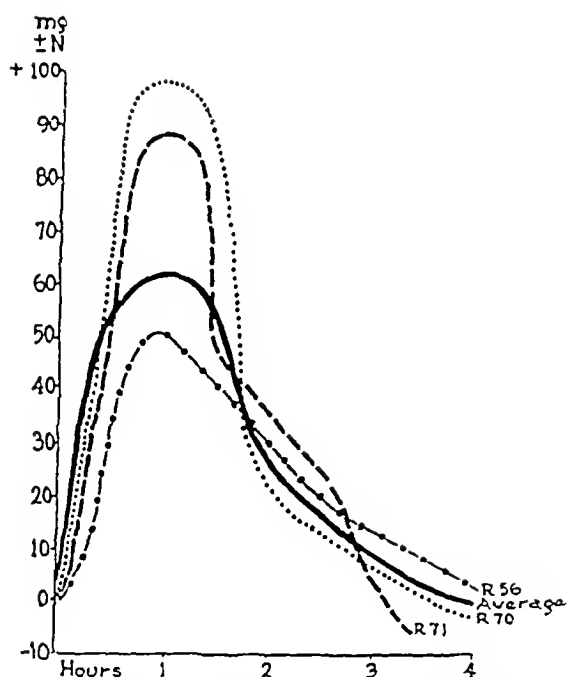
Chart 1.—Changes in the blood cholesterol of rabbits under ether anesthesia.
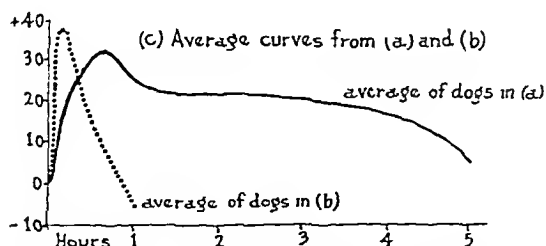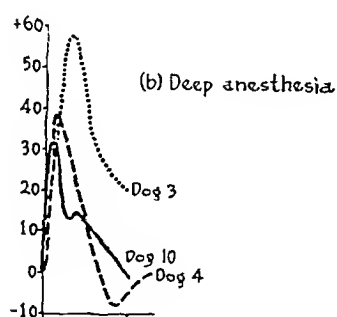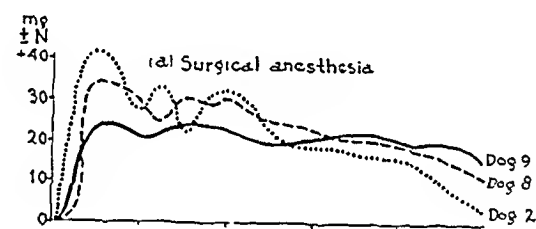
Chart 2.—Changes in the blood cholesterol of dogs under ether anesthesia.

of anesthesia; then a gradual return toward the normal, approaching it after about five hours of anesthesia. This is best illustrated by plotting a curve from the average of all five dogs for each time period, chart 2c. The change from normal is less in dogs than in rabbits, the highest point of hypercholesteremia varying from 18 to 42 mg. The blood cholesterol was found to be sensitive to amounts of ether given. If, at any point during the experiment, the amount of ether was increased, a rise in the blood cholesterol followed. This is illustrated in chart 3 by the terminal rise in dogs due to an increase in the rate of anesthesia to kill the animals, and by the secondary rise in blood cholesterol after an increase in the depth of anesthesia in both dogs and rabbits. Other examples are included in the later section on changes in the blood sugar.
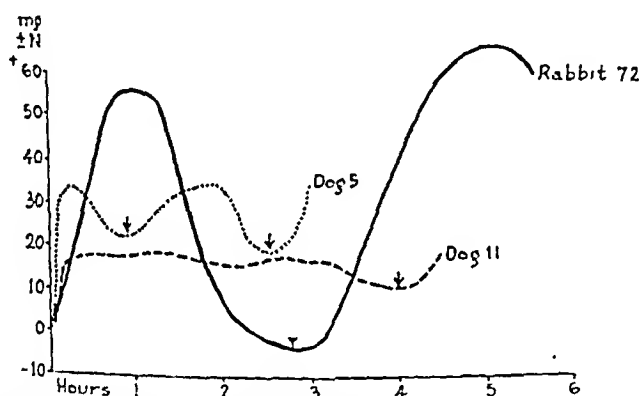
Chart 3.—Changes in the blood cholesterol due to increasing the rate of anesthesia (arrows indicate point of increase).

In three dogs the anesthesia was given much more rapidly, larger amounts of ether being given to produce rapid and deep anesthesia. Chart 2b shows a more rapid rise than in surgical anesthesia, a peak being reached in from five to ten minutes, and a more rapid drop toward normal, which is reached after about an hour of anesthesia. The average of these dogs shows a higher peak as well as a more rapid change.

Two dogs subjected to smaller quantities of anesthetic, so that only partial relaxation was obtained and reflexes were very active, showed a much lower peak and much more fluctuation.

Chloroform Anesthesia: Eight dogs were used. Again three typical experiments are illustrated (chart 4), together with the composite curve averaged from the changes in all eight dogs. The values taken as normal ranged from 127 to 200 mg. per hundred cubic centimeters of blood, some of which are probably higher than the true normal for the dogs. If determinations were made during the first

few minutes of anesthesia, the blood cholesterol was found to fluctuate somewhat, even falling below the values taken as normal, especially if it was rather high. The curves are plotted, using fifteen minutes after the introduction of anesthesia as the initial point of change. A gradual, continuous rise in the blood cholesterol occurred, proportional to the length of anesthesia. Three dogs allowed to recover after the experiment showed a continuing rise in blood cholesterol for at least twenty-
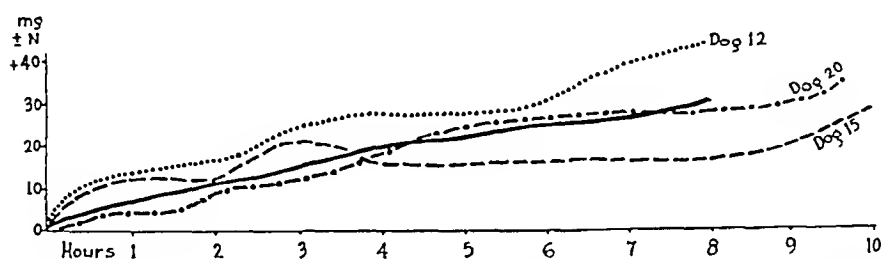
Chart 4.—Changes in the blood cholesterol of dogs under chloroform anesthesia. The heavy black line shows the average for eight dogs.
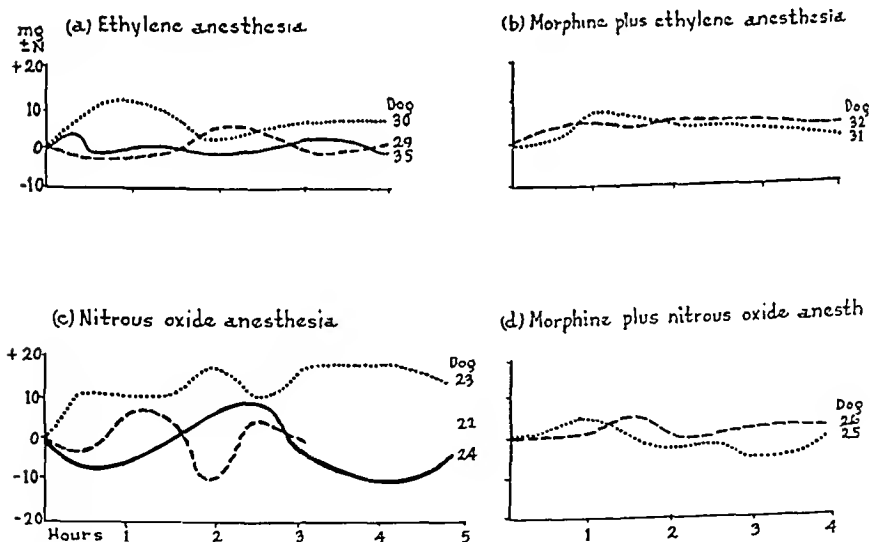
Chart 5.—Changes in the blood cholesterol of dogs under (*a*) ethylene, (*b*) morphine plus ethylene, (*c*) nitrous oxide and (*d*) morphine plus nitrous oxide anesthesia.

four hours. After a week, however, the values were down to normal limits. Table 1 gives the essential figures for one of these experiments.

Ethylene and Nitrous Oxide Anesthesia: Ethylene-oxygen anesthesia alone was found to be rather poor for dogs. It was somewhat difficult to secure a state of good relaxation, and a concentration of 95 per cent ethylene to 5 per cent oxygen was required. Five dogs

were used. The results in three are charted (chart 5) for the first four hours. There was no great change in the blood cholesterol at any period, but a moderate fluctuation was constant. Two dogs given 30 mg. of morphine sulphate subcutaneously about half an hour before the experiment showed much less fluctuation (chart 5*b*).

Nitrous oxide-oxygen anesthesia was found to be even less satisfactory as an anesthetic for dogs; 95 per cent nitrous oxide to 5 per cent oxygen was used. It was difficult to abolish voluntary movements
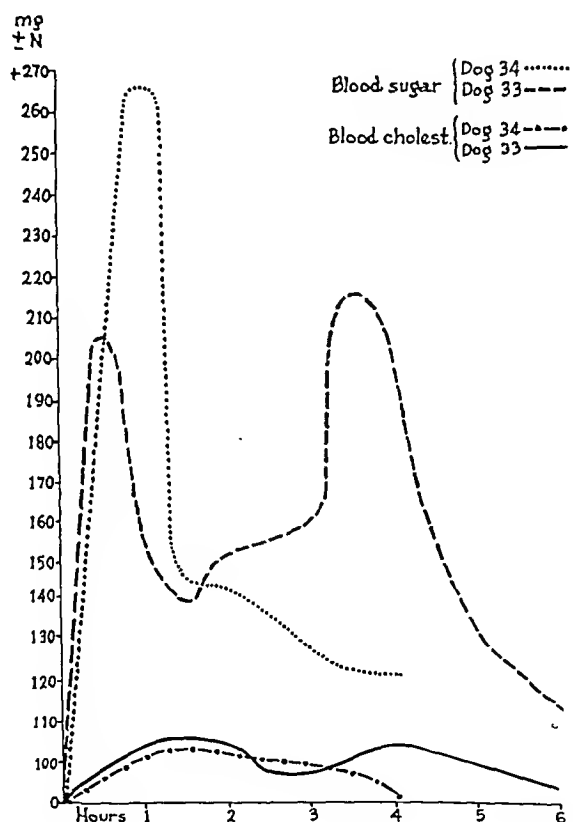
Chart 6.—Changes in the blood sugar and blood cholesterol under ether anesthesia.

TABLE 1.—*Changes in Blood Cholesterol in Chloroform Anesthesia (Dog 16)* *

		Cholesterol, Mg. per 100 Cc.
5/12/31: 1:10 p.m.	Normal blood cholesterol	216
7:45 p.m.	After 6½ hours of chloroform anesthesia	240
5/13 31: 7:30 p.m.	Twenty-four hours after anesthesia	253
5/19/31: 2:25 p.m.	One week after anesthesia	206

* A black male terrier; weight, 10.9 Kg.

and almost impossible to secure complete relaxation. The fluctuations were greater than with ethylene (chart 5c), but here, too, there was no great or constant change in the blood cholesterol. Morphine, given beforehand, diminished the fluctuation markedly and resulted in a minimal change from the normal (chart 5d).
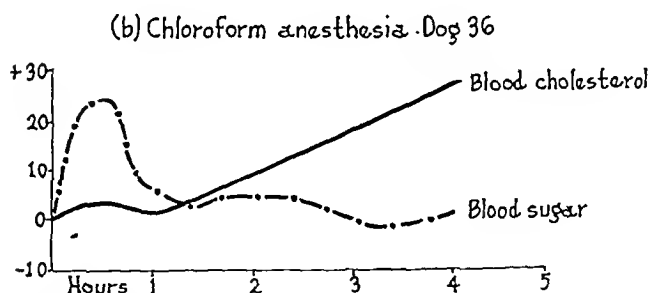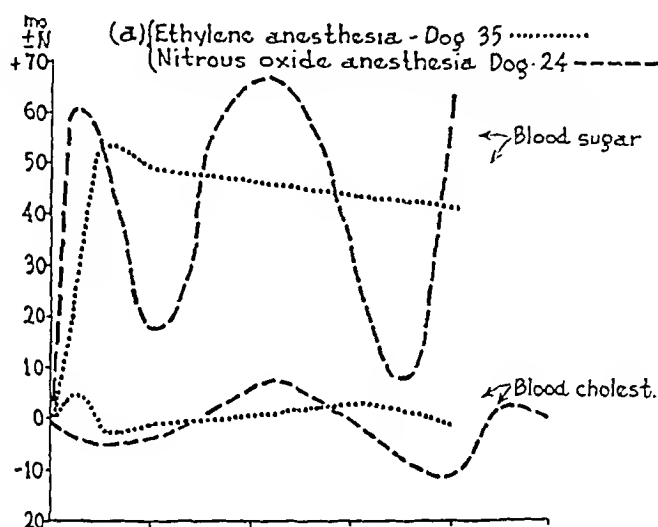
Chart 7.—Changes in the blood sugar and blood cholesterol under (a) ethylene and nitrous oxide anesthesia, and (b) chloroform anesthesia.

Excitement: As has been indicated, some of the changes in blood cholesterol were thought to be due to something other than the anesthetic. On numerous occasions blood drawn when the animal was excited from tying, etc., showed higher cholesterol values than succeeding samples taken after the dog had been quiet for some twenty-five minutes. These changes are shown in table 2. Table 3 shows the changes taking place in a dog before and after excitement from playing and fighting. Excitement was accompanied by a hypercholesteremia

TABLE 2.—*Effect of Excitement on the Blood Cholesterol of Dogs*

Dog	Time		Cholesterol, Mg. per 100 Cc.	Rise, Mg. per 100 Cc.
4	1:30 p.m.	Blood drawn from quiet dog..........................	148	
	1:55 p.m.	Dog excited by presence of cat; then tied down without any attempt at quieting......................	160	12
18	10:40 a.m.	Dog tied to table, causing excitement; blood drawn immediately afterward	210	
	11:55 a.m.	Blood drawn after quieting dog since 10:40..........	200	10
28	9:00 a.m.	Dog tied to table; excited; blood drawn.............	213	
	9:25 a.m.	Blood drawn after quieting dog.....................	202	11

TABLE 3.—*Effect of Excitement on Blood Sugar and Blood Cholesterol in Dog 37* *

Date	Time		Sugar, Mg. per 100 Cc.	Change, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Change, Mg. per 100 Cc.
12/4/31	9:05 a.m.	After playing excitedly for about one hour	141		157	
	10:15 a.m.	After lying quiet for one hour...	112	29	147	10
12/5/31	1:00 p.m.	After spending a morning alone in a quiet room.................	97		142	
	2:30 p.m.	After a fight with another dog, preceded by playing for ½ hour	152	55	159	17
12/7/31	6:50 p.m.	After being alone in a quiet room all afternoon..............	105		139	
	7:30 p.m.	Following 30 min. of tumbling play, pulling, jumping, etc. ...	137	32	148	9
12/8/31	9:30 a.m.	Following 20 min. of play........	131		153	
	11:50 a.m.	After quiet of two hours.........	105	26	147	6

* A pet terrier, very lively but trained to obey. The dog was fed on a diet of meat and bread once a day, in the evening after the completion of the experimentation.

TABLE 4.—*Effect of Excitement on Blood Cholesterol of Rabbits*

Rabbit	Time (10/6/31)		Cholesterol, Mg. per 100 Cc.	Change, Mg. per 100 Cc.
74	2:05 p.m.	Put in box; rather quiet		
	2:15 p.m.	Blood taken	85	
	2:27 p.m.	Blood taken	85	
	2:36 p.m.	Blood taken	83	
		(Average, 84)		
	2:40 p.m.	Removed from box; placed before dogs, chased about, rolled onto back, rolled over and over, etc., for 20 minutes		
	3:00 p.m.	Blood taken	93	8 (rise)
75	3:05 p.m.	Chased about cage, run about floor, rolled, etc., for 15 minutes		
	3:20 p.m.	Blood taken	93	
	3:25 p.m.	Blood taken	93	
	4:20 p.m.	Blood taken	88	
	4:40 p.m.	Blood taken	85	8 (drop)
3-76	4:30 p.m.	Taken from cage and put in box quietly		
	4:45 p.m.	Blood taken	80	
	5:00 p.m.	Blood taken	76	
		(Average, 78)		
	5:05 p.m.	Taken from box; thrown into air, chased (not caught) by a dog, rolled over and over on floor many times, etc., until 5:35 p.m.		
	5:40 p.m.	Blood taken	89	
	5:50 p.m.	Blood taken	88	10 (rise)

averaging about 10 mg. above the normal. Table 4 illustrates similar changes in rabbits with relation to excitement.

2. *Blood Sugar.*—Ether Anesthesia: On two dogs the changes in blood sugar were followed with the blood cholesterol changes. Chart 6 illustrates the changes in the two blood constituents. The blood sugar rose rapidly to reach a peak within the first hour of anesthesia, and then gradually fell toward normal. The blood cholesterol, changing much less, showed a slightly slower but similar response. Dog 33 also illustrates the effect of changes in the depth of anesthesia. After one and a half hours of anesthesia, the amount of ether being given was slightly increased. At the end of three hours of anesthesia, the ether bottle was refilled, resulting in a temporary increase in the amount of anesthesia given. The corresponding rise in both blood sugar and blood cholesterol values is apparent.

Other Anesthetics: Under chloroform anesthesia the change in blood sugar was similar to that under ether: a rapid rise and a gradual fall to normal, in spite of the fact that the blood cholesterol continued to rise (chart 7*b*). Under ethylene and nitrous oxide anesthesia the blood sugar showed the same rapid rise, with subsequent fluctuation about this elevated point (chart 7*a*).

Excitement: Table 3 demonstrates the rise in blood sugar after excitement not related to anesthesia.

COMMENT

Mann[6] suggested that the initial rise in blood cholesterol under ether anesthesia might be due to excitement. Excitement must play some part in the hypercholesteremia. Lyons[14] has recently reported an emotional hypercholesteremia in cats: an increase in blood cholesterol of from 25 to 30 per cent after from twenty to forty minutes of excitement. This change was absent after the removal of the sympathetic nervous system. But this factor does not seem to be entirely responsible. The excitement stage under all the anesthetics used was similar, yet the rise of blood cholesterol under ether was greater than under the others. Then, too, excitement without anesthesia produced less change than occurred with the anesthesia. Dog 11 (chart 3) received barbital before the ether anesthesia. Excitement was eliminated, and the rise was less marked but not absent. Dog 4 (table 2) was anesthetized immediately after the excitement experiment, and by comparison with chart 2*b* it will be seen that ether anesthesia was accompanied by a greater hypercholesteremia than occurred with excitement in the same dog.

14. Lyons, C.: Am. J. Physiol. **98**:156, 1931.

The fact that blood sugar rises under anesthesia is well established. All authors do not agree as to the type of change. Macleod [15] thought that the changes in the dextrose content of the blood from anesthesia were slight. Ross and McGuigan [16] stated the increase in blood sugar to be general and consistent, and demonstrated a continuance of the high sugar content of blood after the cessation of anesthesia. Their periods of anesthesia lasted two hours. Examination of their tables shows some values still rising after two hours, but others have already reached a peak at one hour and are lower after two hours. The after rise may be associated with excitement as consciousness returns. Sansum and Woodyatt,[17] working with phlorizinized dogs, found an initial increase in blood sugar with ether and with chloroform, followed by a fall. Nitrous oxide failed to produce such changes. Mahler [7] reported a continuous rise in blood sugar under ether anesthesia for periods of one hundred minutes. Mackay and Dyke [18] found a rapid initial rise, with a gradual return to the original level. Trout [19] has reported a postoperative increase in blood sugar after twenty minutes of ethylene anesthesia.

The cause of the hyperglycemia is still more disputed. In 1910, Macleod and Pearce [20] demonstrated a reduction in the glycogen content of the liver following ether anesthesia. Shaffer [21] thought that the rise in sugar was due to excitement and asphyxia, but King, Moyle and Haupt [22] had previously eliminated asphyxia by producing the anesthesia by intravenous injection of ether, and still obtained a hyperglycemia. Ross and McGuigan [16] felt that the effect was not due to excitement or asphyxia but to the ether itself acting as an activator on liver glycogen, permitting the action of diastase on it. However, Stewart and Rogoff,[23] working with adrenalectomized rabbits, found a greater increase in blood sugar from asphyxia superimposed on ether anesthesia than from the anesthesia alone. Ross and Davis [24] suggested that ether hyperglycemia might be due to depression of the internal secretion of the pancreas, and Mahler [7] used this theory to explain the absence of the rise in blood sugar on the subcutaneous injection of

15. Macleod, J. J. R.: Diabetes: Its Pathological Physiology, New York, E. Arnold, 1913, p. 187.

16. Ross, E. L., and McGuigan, H.: J. Biol. Chem. **22**:407, 1915.

17. Sansum and Woodyatt: J. Biol. Chem. **21**:1, 1915.

18. Mackay, R. L., and Dyke, S. C.: Brit. J. Anæsth. **6**:61, 1928.

19. Trout, H. H.: Anesth. & Analg. **8**:269, 1929.

20. Macleod, J. J. R., and Pearce, R. G.: Am. J. Physiol. **27**:341, 1910-1911.

21. Shaffer, P. A.: J. Biol. Chem. **19**:297, 1914.

22. King, Moyle and Haupt: J. Exper. Med. **16**:178, 1912.

23. Stewart, G. N., and Rogoff, J. M.: J. Pharmacol. & Exper. Therap. **15**:238, 1920.

24. Ross, E. L., and Davis, L. H.: Am. J. Physiol. **53**:391, 1920.

insulin previous to anesthesia. Fuss[25] believed ether hyperglycemia due to mobilization of sugar from the liver. Rosenthal and Bourne[26] found that hepatic function was diminished after anesthesia, and Cantarow and Gehret[27] cited clinical material demonstrating that patients with hepatic disease do not show a rise in blood sugar under ether as other patients do.

It seems most probable that the hyperglycemia is due to increased hepatic glycogenolysis. Ether itself must play a part in this process, since it is accompanied by a rise so markedly greater than that of excitement alone. The hyperglycemia occurring in chloroform, ethylene and nitrous oxide anesthesia is much less in amount and may very well be due to excitement, which alone can lead to a rise in blood sugar equal to that from these anesthetics. It has been shown that in ether anesthesia the changes in blood sugar and in blood cholesterol tend to parallel each other. Then, if the change in blood sugar is due to increased mobilization from the liver, may not at least part of the increased amount of cholesterol in the blood have the same origin?

Insulin prevents the rise of both these blood constituents under anesthesia. Remesow and his co-workers[28] have recently found that while cholesterol leads to glycogenolysis in the liver, cholesterol plus insulin results in the storage of glycogen in the liver. In anesthesia the effect may be due, as stated, to a suppression of the internal secretory function of the pancreas, and if insulin is given artificially it may nullify the glycogenolysis by its power to increase storage.

However, the hypercholesteremia cannot be attributed entirely to loss of lipoid from the liver. Other organs also release cholesterol into the blood. Manceau[9] reported a considerable diminution in the cholesterol content of the adrenal gland from chloroform anesthesia. After the administration of ethyl alcohol to dogs over a period of days, Ducceschi[29] found a constant decrease in the cholesterol content of the adrenal gland averaging 40 per cent, and sometimes a decrease in other organs, such as the testis.

The gradual drop in hypercholesteremia after an hour's anesthesia may be due to the gradual lowering of the amount of cholesterol easily separated from the tissues. Since ether does not produce much toxic

25. Fuss, H.: Klin. Wchnschr. **9**:410, 1930.

26. Rosenthal, S. M., and Bourne, W.: The Effect of Anesthetics on Hepatic Function, J. A. M. A. **90**:377 (Feb. 4) 1928.

27. Cantarow, A., and Gehret, A. M.: Ether Hyperglycemia, J. A. M. A. **96**:939 (March 2) 1931.

28. Remesow and Matrossowitsch: Ztschr. f. d. ges. exper. Med. **77**:67, 1931. Remesow, Matrossowitsch and Sepalowa: ibid. **77**:100, 1931.

29. Ducceschi, V.: Arch. ital. de biol. **70**:93, 1920.

degeneration, cholesterol from that source is not liberated, and as removable cholesterol diminishes in the tissues, the blood cholesterol falls to or below normal.

The change in the cholesterol content in chloroform anesthesia is more easily explained. The initial changes are of the same magnitude as the changes with excitement, and may be attributed to that factor (dog 18, table 2). The gradual but continuous rise in blood cholesterol with continuous chloroform anesthesia is, perhaps, the result of toxic degeneration of the liver cells with liberation of the lipoid substances, increasing in amount as the destruction of the tissue proceeds. In 1909, Howland and Richards [30] suggested this as the cause of the after rise of blood lipoids following chloroform poisoning.

The fluctuations in blood cholesterol found throughout ethylene and nitrous oxide anesthesia are of the same magnitude as those produced by excitement and, as with the hyperglycemia, may be attributed entirely to it, especially since these gases fail to produce a good anesthetic state in the dogs. The diminution of the fluctuations when morphine precedes the anesthesia also indicates that excitement is the main factor in the changes.

Although it was known that ether anesthesia is attended by a hypercholesteremia, Mann [6] alone noted that this is temporary and is followed by a drop to normal under continued anesthesia. He attributed the rise to excitement. This report gives evidence that although excitement is a factor, ether itself is responsible for a transient but not continued hypercholesteremia, and that the more generally known changes in blood sugar are proportional to the lipoid changes. Chloroform anesthesia has been reported as producing no rise (Bloor [2] and Lattes [8]), a slight rise (Ducceschi [5] and Manceau [9]) and a great rise (Reicher [3]) in acute experiments. An after rise has been found constantly. The experiments in this paper show an absence of immediate change but a gradual, continuous rise proportional to the length of anesthesia. The after rise is also noted. Under nitrous oxide anesthesia, Manceau [9] found a slight rise in the blood cholesterol of monkeys. According to Mahler,[7] patients previously given morphine showed no rise in blood cholesterol under nitrous oxide. The data here presented show no changes due to nitrous oxide. An investigation of the literature revealed no studies of the blood cholesterol under ethylene anesthesia. This report indicates that ethylene has no effect on the blood cholesterol.

The differences in previously reported results on changes in blood sugar and blood cholesterol under various anesthetics can be attributed largely to a factor seldom considered, that of excitement. Shaffer [21] and Mann [6] suggested that excitement affected the blood sugar, and Lyons [14]

30. Howland, J., and Richards, J.: J. Exper. Med. **11**:344, 1909.

showed for the first time (1931) that emotion disturbed the blood cholesterol. The experiments reported in this paper demonstrate that excitement in rabbits and dogs causes both a hyperglycemia and a hypercholesteremia, and that the excitement seems to be responsible for the changes in blood sugar and the acute changes in blood cholesterol under chloroform, nitrous oxide and ethylene anesthesias.

Chloroform and ether anesthesia disturb the lipoid metabolism, and ether affects the carbohydrate metabolism as well. Nitrous oxide and ethylene—of more import because of its wider applicability—disturb neither lipoid nor carbohydrate metabolism, and seem therefore to be more physiologic anesthetics.

SUMMARY

1. Continuous ether anesthesia in dogs and rabbits is accompanied by a hypercholesteremia that, in ordinary surgical anesthesia, reaches a peak in from sixty to ninety minutes and thereafter gradually diminishes in amount, returning to approximately normal limits in from four to five hours.

2. Continuous chloroform anesthesia is accompanied by slight immediate change but by a gradual and continuous rise in the blood cholesterol proportional to the duration of anesthesia (up to ten hours).

3. Ethylene and nitrous oxide anesthesias are accompanied by no changes in the blood cholesterol other than those explainable by excitement and imperfect anesthesia.

4. Excitement is accompanied by a hypercholesteremia. This factor increases, but is not entirely responsible for the change found under ether anesthesia. It seems to be responsible for initial changes under chloroform and for the irregularity in the blood cholesterol values under ethylene and nitrous oxide.

5. Ether anesthesia is also accompanied by a hyperglycemia that frequently tends to be proportional to the hypercholesteremia. Chloroform, ethylene and nitrous oxide anesthesia are accompanied by a hyperglycemia, as is excitement without anesthesia.

6. Ethylene and nitrous oxide, as anesthetics, seem to be more physiologic in their action than ether and chloroform.

FIFTIETH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Congenital Malformations of the Hand.—Kanavel,[1] in two excellently illustrated monographs, presented the complex group of congenital malformations of the hand. From a review of the literature and of his own cases he concluded that the cases were usually hereditary, and that they arose from a defect or an injury to the germ plasm. He illustrated the common types and discussed their treatment in detail. Any one attempting plastic surgical procedures in these cases should be thoroughly conversant with Kanavel's technic.

Congenital Dislocation of the Hip.—Dickson[2] divided congenital dislocations of the hip into three groups according to the age in which they occur: (1) those occurring in patients less than 4 years of age, (2) those occurring in patients between 4 and 9 years and (3) those

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This report of progress is based on a review of 177 articles selected from 337 titles appearing in the medical literature approximately between July 30, 1932, and Nov. 21, 1932. Only the papers that seemed to represent progress have been selected for review.

1. Kanavel, A. B.: Congenital Malformations of the Hands, Arch. Surg. 25:1 (July); 282 (Aug.) 1932.

2. Dickson, F. D.: Surg., Gynec. & Obst. 55:81, 1932.

occurring in patients over 9 years. He expressed the belief that in the majority of cases in patients under 4 years of age the dislocation can be reduced by a closed manipulation, but that occasionally open reduction is necessary. It is his opinion, further, that congenital dislocation of the hip in children older than 4 years should usually be treated by open operation, that many of the dislocated hips in children between 4 and 9 years can be reduced, and that in some of the children beyond this age the hips can be successfully restored to their normal position. Many of the hips, however, require some other type of operation, and he advocates the shelf operation for the older children. He outlined his technic for this operation. Preceding the operation, he applies skeletal traction for two weeks. Briefly, a wide anterior approach is used. A shelf which extends well anteriorly and posteriorly is turned down from the ilium just above the head of the femur. A wedge of bone is taken from the region of the anterior superior spine and wedged between the shelf and the ilium. The entire operation is performed under traction, which is maintained for six weeks afterward. In 21 of 26 shelf operations, he obtained good results; 2 patients were improved, and in 3 the operations were failures.

POLIOMYELITIS

Early Diagnosis and Treatment of Poliomyelitis.—Macnamara and Morgan,[3] as a result of their experience in the treatment of infantile paralysis, concluded that it is possible to diagnose poliomyelitis in the preparalytic stage. In their cases, the preparalytic stage lasted from two to seven days; rarely was the onset fulminating. The use of human immune serum gave excellent results. They insist on the importance of examining the cerebrospinal fluid at the bedside of the patient, so that serum can be administered immediately if the diagnosis is positive. The initial dose of serum was 50 cc., part being given intrathecally and part intravenously. If the dose was adequate, the temperature fell and the general condition improved. If improvement was not marked within eighteen hours, the dose was insufficient, and from 20 to 40 cc. more was injected intravenously. Of the series of 133 patients, 7 only, in their opinion, were not benefited; they attributed these failures to insufficient dosage, or to the delay between the withdrawal of the cerebrospinal fluid and the administrations of the serum.

Poliomyelitis, a Preliminary Report of 98 Cases.—During the 1931 epidemic of poliomyelitis, 98 patients were studied by Kramer[4] in the Jewish Hospital, Brooklyn. Ninety per cent of the cases were in chil-

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3. Macnamara, J., and Morgan, F. G.: Lancet **1**:469 (Feb. 27); 527 (March 5) 1932.

4. Kramer, B.: New York State J. Med. **32**:855, 1932.

dren less than 10 years of age. A diagnosis was made in 54 cases before paralysis appeared. The incidence of paralysis in patients treated with convalescent serum was certainly not less than that in the untreated patients. The Drinker respirator was used in 10 cases. The author concluded that the respirator is of value only in the spinal type of paralysis, and not in the bulbospinal or the bulbar type. Forty-six, or 47 per cent of the patients, recovered completely.

[ED. NOTE.—Any new treatment passes through a stage of enthusiastic support before a correct appraisal of its value is secured. The present opinion regarding the use of convalescent serum seems to be somewhat less optimistic than formerly.]

Epidemic of Poliomyelitis.—Peck[5] made a statistical report of the 1931 epidemic of poliomyelitis in New York State; 4,080 cases were reported from July 1 to Nov. 1, 1931. Seventy-six per cent of the patients received treatment in a hospital. Eleven per cent of the patients died, whereas in 1916, 27 per cent died. Paralysis developed in only 17, or 0.5 per cent of the patients treated in hospitals for contagious diseases during the preparalytic stage. Boys were affected more often than girls. Fifty-three per cent of the patients were under 5 years of age; 31 per cent were under 10 years, and only 3 per cent were over 20 years. The majority of persons affected were born after the 1916 epidemic. This, the author thought, spoke for generalized acquired immunity. Only 6 of the 4,080 cases could be considered to be caused through contact.

TUBERCULOSIS

Tuberculous Spondylitis Treated at Bammelwerd, Germany, Between 1912 and 1930.—Reinhart[6] reviewed the cases of 91 patients with tuberculosis of the spine, 74 of whom had been discharged or had died and 17 of whom were still under treatment at the time of writing. Most of the lesions were in the lower dorsal part of the spine or in the upper lumbar part. The twelfth dorsal vertebra was most frequently involved. In 42 per cent of the cases the disease began in patients between the ages of 16 and 25. Forty-seven per cent of the patients were in the first two decades of life. Fifty-six of the 91 patients (61 per cent) had abscesses. Men (74.5 per cent) were affected more often than women. Thirty per cent of all the patients observed and 50 per cent of those with abscesses had fistulas; half of the fistulas had followed surgical incision. Deformity was present in 54 of the 91 patients (59 per cent). Lesions from the seventh dorsal to the second lumbar vertebra caused the worst deformities. The

5. Peck, H. T.: New York State J. Med. **32**:854, 1932.
6. Reinhart, M.: Beitr. z. Klin. d. Tuberk. **79**:745, 1932.

severest types were seen in female patients and in patients in whom the condition started in childhood. Pulmonary lesions were present in 22 patients (24 per cent). Extrapulmonary lesions were found in 20 of the 91 patients (22 per cent). In 16 of these 20, the spinal lesion and the other lesion appeared simultaneously. Renal tuberculosis and glandular tuberculosis were the commonest. Tuberculous exposure in the family was noted in 38 cases, or 41 per cent. The sedimentation time was determined in 15 uncomplicated cases: in 9 the results were normal. Of 21 patients with abscesses, 13 showed marked acceleration of the sedimentation time, and only 2 had a normal rate. All varieties of treatment were employed, but mainly conservative. In 12 patients, spinal fusions were performed. The author was of the opinion that the statistics of the deformity and mortality were unaltered by the operations in these few cases. The conditions of the 72 patients who were discharged were as follows: clinically healed, 47 (55.3 per cent); improved, 10 (13.9 per cent), and unimproved, 11 (15.3 per cent). Four patients died at the hospital (5.5 per cent). Of twenty-six patients with closed abscesses, 4 (15 per cent) died. The author agreed with Calot that scalpel opening causes a catastrophe. Of the 58 patients still living, 46 were capable of full work; 8 were capable of limited labor, and 4 were incapable of labor.

Culture of Tubercle Bacilli from Blood According to Löwenstein's Method in Tuberculosis of the Bones.—Urgoiti,[7] following in a general way the method devised by Löwenstein, attempted to culture tubercle bacilli from the blood of patients suffering from tuberculosis of the bones. A tuberculous bacillemia was believed to be present in cases in which there was active tuberculosis. The author described in detail the technic used. In 26 of 67 cases of tuberculosis of the bones, cultures of tubercle bacilli were recovered from the blood. There were 10 positive cultures in 20 cases of pulmonary tuberculosis.

Tuberculous Bacillemia.—Gualdi[8] used the method of Löwenstein in attempting to isolate tubercle bacilli from the blood of patients who were suffering from various forms of tuberculosis. A number of studies were also made on patients with rheumatic infections. The author was able to obtain only 1 positive culture of tubercle bacilli in 30 tuberculous patients. All of the blood cultures in cases of rheumatic infection were negative. The difficulty of isolating tubercle bacilli from the blood was stressed. The author did not feel that his results indicated the absence of tuberculous bacillemia.

7. Urgoiti, A.: Beitr. z. Klin. d. Tuberk. **80**:480, 1932.
8. Gualdi, A.: Policlinico (sez. chir.) **39**:493, 1932.

[ED. NOTE.—The recovery of tubercle bacilli from the blood in tuberculosis of the bones and joints is of considerable importance and stresses the importance of both general and local measures in treatment.]

Roentgen Signs of Tuberculosis of the Vertebral Body.—Daub and Badgley [9] studied the roentgen appearance of the vertebral body in 100 cases of tuberculosis of the spine. They were able to distinguish three types of lesions: a central type, an intervertebral articular type and an anterior type. The central type showed the lesion in the midportion of the vertebral body. Infection occurred most probably through the posterior spinal arteries. This was the usual type observed in children. It was more common in the dorsal region. Collapse of the vertebral body and severe deformity were observed chiefly in this type. The intervertebral articular type of infection probably occurred through the epiphyseal arteries. The infection was chiefly on the disk side of the vertebral body. Here a spread to the intervertebral disk occurred early with rapid narrowing of the disk, while the vertebral body remained intact until late. This type was more common in the lumbar region. In the anterior type the infection was along the anterior surface of the vertebral body. The infection probably spread through the intercostal arteries. The author found narrowing of the intervertebral disks to be the earliest and most constant sign of vertebral tuberculosis. Abscess was the most common complication, occurring in 84 per cent of the cases. Double lesions with intervening normal vertebrae were found in 10 per cent of the patients. Tuberculosis in other parts of the body was seen in 52 per cent of the patients. Pulmonary tuberculosis was present in 24 per cent of the patients.

[ED. NOTE.—Several of the editors have observed these three types of vertebral lesions in tuberculosis, but they have considered the central type to be the least common, especially in children.]

PYOGENIC INFECTIONS

Maggots in Osteomyelitis.—Buckman and Blair [10] carried on Baer's method of treatment of osteomyelitis by means of maggots, with certain modifications. Their work has contributed definitely to the clinical and laboratory technic and to the knowledge concerning this procedure. They concluded that maggots do not eat, destroy or remove dead bone, and that for this reason operative treatment should be adequate. They suggested that the proliferation of healthy granulation tissue is due to the mechanical stimulation of the incessantly crawling maggots. They concluded that the treatment, though more costly, is not so time-con-

9. Daub, H. P., and Badgley, C. E.: Am. J. Roentgenol. 27:827, 1932.

10. Buckman, J., and Blair, J. E.: Surg., Gynec. & Obst. 55:177, 1932.

suming as dakinization and is superior to the "Orr technic" in that healing takes place more rapidly, gives better scars and does not, as a rule, necessitate prolonged periods of immobilization in plaster of paris.

Pathologic Fractures in Osteomyelitis.—Capener and Pierce [11] called attention to the not infrequent occurrence of fractures following osteomyelitis, and stated that at the University of Michigan this complication had occurred in 1.66 per cent of 1,086 cases, and that the fractures represented one third of all pathologic fractures of the long bones. Delayed recognition of the disease with subsequent diaphyseal sequestration, long-standing atrophy from disuse and overzealous removal of bone when "saucerizing" a cavity were considered the chief causes of such fractures. The authors emphasized the importance of preventing these disasters by splinting the extremity during convalescence.

[ED. NOTE.—In view of the frequency of pathologic fracture in osteomyelitis, it is important to emphasize that the presence of the disease is not incompatible with healing of the fracture. Union has been obtained by prolonged splinting in the experience of several of the editors.]

NEOPLASMS

Skeletal Metastases in Hypernephroma.—Lehmann,[12] in an exhaustive review of the Germanic literature on metastasis in hypernephroma, called attention to several important aspects of the problem. It was Helferish who in 1887 reported metastases to the bone as the first symptom of a silent tumor of the kidney, occurring long before the primary renal tumor occasioned any attention. The occurrence of such distant metastases, often solitary for a long time, has led to their excision, sometimes with the impression that they were primary tumors of the bone, and sometimes with a knowledge of their true character. If the solitary metastasis and the primary tumor of the kidney are both excised, life in certain cases may be definitely prolonged. In a follow-up study of 9 patients so treated, the duration to death was found to be one year in 1, one and one-half years in 1, two years in 3, from five to six years in 3 and twelve years in 1. The author believes that at least one third of the cases of metastases from hypernephroma were cases of solitary metastasis at first. He was inclined to attribute the frequency of metastasis to the flat bones to the narrowness of the capillaries in the red marrow present in the flat bones of the adult.

Osteitis Fibrosa.—Lang [13] stated that osteitis fibrosa is a secondary condition of the bone dependent on circulatory disturbances in bones

11. Capener, N., and Pierce, K. C.: J. Bone & Joint Surg. 14:501, 1932.
12. Lehmann, W.: Arch. f. klin. Chir. 170:331, 1932.
13. Lang, F. J.: Am. J. Path. 8:263, 1932.

following either trauma without tearing of the periosteum or functional bending and cracking of the skeleton because of insufficient calcification (rickets, scurvy and osteomalacia). Occasional occurrence of osteitis fibrosa associated with tumors of the parathyroid gland does not contradict the concept which regards osteitis fibrosa as a secondary process in bone dependent on osseous circulatory disturbances.

[ED. NOTE.—The concept that osteitis fibrosa and giant cell tumors are due to functional circulatory disturbances is not new. Of great importance, however, is the emphasis placed on the occasional but not constant association of osteitis fibrosa and tumors of the parathyroid gland.]

Giant Cell Tumor.—Kirklin and Moore [14] reviewed the roentgen appearance in 86 proved cases of giant cell tumor and classified them into two types: 1. The first was the usual variety described in all textbooks as a central tumor situated most often in the end of a long bone, exhibiting trabeculation and expanding, but not breaking through the cortex. 2. "Trabeculation was conspicuously absent. The roentgenograms gave evidence of homogenous lysis of the affected area: the cortex was not only expanded but was dissolved wholly or in part, and the tumor projected into the soft tissues. This variety might be mistaken for primary sarcoma or a massive metastatic growth."

Roentgen Treatment of Giant Cell Tumor.—Pfahler and Parry [15] reviewed the roentgen treatment of giant cell tumors in 26 cases; 1 patient was reported as being the first one (1906) ever to be treated in this way. They concluded that fractional dosage with high voltage roentgen rays is the method of choice and is superior to surgical intervention or to a combination of the two. All of their patients gave a satisfactory response, and none died of a malignant process.

Peirce [16] reported 2 cases of apparent malignant degeneration of giant cell tumors. He agreed with Pfahler and Parry as to the treatment.

[ED. NOTE.—Opinion is still divided as to the relative merits of irradiation and operation in the treatment of giant cell tumors. Cure by irradiation requires a longer time and necessitates prolonged observation of the patient.]

Diseases of the Bone After Roentgen Treatment for Uterine Carcinoma.—Philipp [17] reported a series of observations on the patho-

14. Kirklin, B. R., and Moore, C.: Am. J. Roentgenol. 28:145, 1932.

15. Pfahler, G. E., and Parry, L. D.: Am. J. Roentgenol. 28:151, 1932.

16. Peirce, C. B.: Am. J. Roentgenol. 28:167, 1932.

17. Philipp, E.: Strahlentherapie 44:363, 1932.

logic changes which occurred in the femora after roentgen and radium therapy for carcinoma of the uterus. There was a gradual decalcification particularly in the necks of the femora which, the author was convinced, was not due to metastases. He suggested that a change in the blood vessels as a result of the large amount of irradiation probably played a rôle in the decalcification. Five cases were reported in detail. In 1 case, coxa vara developed on both sides. In 2 cases, fracture of the femoral neck was observed. Fracture of the neck of the femur was seen on both sides in 1 case. In the fifth case, there was a loss of cartilage in the hip joint, with stiffening of the joint after irradiation; no inflammatory lesion could be demonstrated in the hip. These changes occurred from two to nine months after irradiation. The author could find no similar reports in the literature. He believed that poorer technic in the past led to less rapid changes, and that the patients usually died of metastasis before such conditions could be recognized. The relation of these findings to medicolegal cases was discussed.

Reaction of Muscle Tissue to Tumor.—Leadingham's [18] photomicrographs demonstrated the apparent stimulation and elongation of the nuclei of striated muscle by contiguous neoplastic tissue. The nuclei, or muscle corpuscles, increased in number and apparently extended through the sarcolemma in spite of concomitant atrophy and degeneration of the muscle fibers. Sokolow and Fujunami were quoted as having made similar observations. A biologic stimulation of the muscle corpuscles seemed to occur owing to the presence of the neoplastic tissue, and these corpuscles entered into the neoplasm.

[ED. NOTE.—A practical inference may be drawn, namely, that when muscle is involved by a neoplasm, wide and careful excision of the contiguous muscle tissue must be done.]

THE BACK

Reduced Lumbosacral Joint Space.—Of a series of 80 patients with signs of sciatic irritation studied by Williams,[19] 79 per cent had narrowing of the lumbosacral disk as shown by roentgenograms. Anteroposterior roentgenograms were taken with the hips flexed and the lumbar spine flattened. In most cases there was a history of sudden strain with pain in the lower part of the back. Confinement to bed brought temporary relief only. Subsequent attacks were accompanied by pain radiating down the course of the sciatic nerve on one or both sides, corresponding chiefly to the distribution of the fifth lumbar nerve.

18. Leadingham, R. S.: Am. J. Cancer **16**:556, 1932.

19. Williams, P. C.: Reduced Lumbosacral Joint Space: Its Relation to Sciatic Irritation, J. A. M. A. **99**:1677 (Nov. 12) 1932.

Twelve patients had only symptoms in the lower part of the back without radiating pain. The author believes that the probable cause of this condition was rupture of the nucleus pulposus. Congenital narrowing of the disk is considered unlikely, as no evidence of such a condition was found in 300 roentgenograms of persons in early life. The rupture is believed to have been the result of continued physiologic trauma on an intrinsically weak region. The root pain is believed to have been due to changes following the rupture rather than to the rupture itself. Constriction of the intervertebral foramina followed loss of the joint space. This produced compression of the fifth lumbar nerve segment. Another source of nerve irritation was a hypertrophic fringe resulting from abnormal stresses following the loss of the intervertebral space. The treatment indicated was fixation of the lumbosacral joint either by conservative measures or by operation.

[ED. NOTE.—We believe that Williams has made a contribution in calling attention to the narrowed lumbosacral joint space. The weakness of his paper lies in the fact that he did not exclude other lesions producing symptoms in this region.]

CHRONIC ARTHRITIS

Ferment Theory of Arthritis.—Podkaminsky [20] suggested that the immediate cause of arthritis deformans lies in a disturbance of the activities of the ferments of the synovial fluids. This disturbance causes the accumulation of materials which interferes with the normal absorbing and secreting activities of the synovial lining of the joint. The intra-articular cartilage therefore is poorly nourished, its elasticity suffers, and chronic trauma affects the subchondral bone and soon leads to proliferative changes. In the development of spondylitis deformans the nucleus pulposis plays the part of the joint cleft, while the disks and the end-plates play the part of the joint cartilage.

[ED. NOTE.—In this as well as in previous papers the author's theories and experimental studies are of interest in attempting to explain the early physiologic disturbances. Unfortunately, so far they are only theories.]

Knotty Articulations of the Fingers.—Hissard [21] reported 19 cases of articular enlargement of the fingers. The patients had a fusiform swelling of the interphalangeal and metacarpal-phalangeal joints resembling that seen in cases of chronic atrophic arthritis. The photographs accompanying the article could certainly be considered to be those of the hands of patients suffering from atrophic arthritis. Twelve of the

20. Podkaminsky, N. A.: Arch. f. klin. Chir. **171**:592, 1932.
21. Hissard, M.: Ann. de dermat. et syph. **3**:806, 1932.

19 patients had hereditary syphilis, 6 probably had it, while 1 did not have sufficient stigmas to make the diagnosis probable. While the gross appearance of the hands was identical with that seen in chronic atrophic arthritis, the resemblance ended there. There was no pain in the joints on active or passive motion. Motion was limited only slightly. There was no deformity or disalinement of the joints. The patients were unable to state when the condition appeared, and some were not aware of it until it was called to their attention. None of the patients, however, were under 15 years of age. The roentgenograms taken in 5 cases showed no abnormalities. There did not seem to be any connection between the condition of the patients and the chronic rheumatism sometimes seen in hereditary syphilis. This condition was confined to the fingers. There were no general symptoms, fever, pain or roentgenographic changes elsewhere in the skeleton. The beginning of the condition was not known, although various factors, such as the onset at puberty and findings suggestive of acromegaly, led the author to the hypothesis that the "knotty arthritis" might be due to endocrine disturbances secondary to hereditary syphilis.

Disturbances of Growth in Chronic Arthritis in Children.—These disturbances were studied by Kuhns and Swaim,[22] who believe that they are due chiefly to the involvement of the proliferating epiphyseal cartilages by the arthritis, resulting in early ossification. Three types of involvement of growth were noted: persistence of infantile proportions in the hands and feet, shortness of an extremity or a portion of an extremity and, rarely, dwarfism. These sequelae emphasized the need for meticulous management of the young arthritic patient.

[ED. NOTE.—This condition is probably more common in the arthritides of childhood than is commonly appreciated.]

Monarticular Arthritis, Simulating Tuberculosis.—From March, 1924, to January, 1930, Smith [23] encountered 24 cases of monarticular arthritis in which an accurate diagnosis could not be made after a careful study of the history, the results of physical examination, the roentgenograms, the analysis of the blood and the tests with tuberculin. Biopsy and inoculations into guinea-pigs were necessary to establish a diagnosis. Even at biopsy it was not possible to rule out tuberculosis on the gross appearance of the synovial membrane. Careful study of the microscopic sections and inoculations into guinea-pigs or cultures furnished the only accurate diagnostic criteria.

(To be Concluded)

22. Kuhns, J. G., and Swaim, L. T.: Disturbances of Growth in Chronic Arthritis in Children, Am. J. Dis. Child. **43**:1118 (May, pt. 1) 1932.

23. Smith, A. D. DeF.: Monarticular Arthritis Simulating Tuberculosis: A Clinical and Pathologic Study of Twenty-Four Cases, Arch. Surg. **25**:54 (July) 1932.

THERAPEUTIC CONSIDERATIONS IN THE MANAGEMENT OF ACUTE INTESTINAL OBSTRUCTION

TECHNIC OF ENTEROSTOMY AND A FURTHER ACCOUNT OF DECOMPRESSION BY THE EMPLOYMENT OF SUCTION SIPHONAGE BY NASAL CATHETER

OWEN H. WANGENSTEEN, M.D.

MINNEAPOLIS

PHYSIOLOGICOPATHOLOGIC CONSIDERATIONS

The work of Hartwell and Hoguet[1] establishing the efficacy of subcutaneous administration of saline solution in definitely prolonging the lives of dogs with high intestinal obstruction lent considerable impetus to the experimental investigation of obstruction of the bowel. Unfortunately, a like interest in the field has not been generally manifest among clinicians, with the unhappy effect that results in the management of acute intestinal obstruction have not kept astride with increases in knowledge concerning the subject.

The experimental work of the decade following the observation of Hartwell and his associates dealt largely with the nature of the toxin in high intestinal obstruction and a study of the chemical alterations in the blood attending obstruction of the bowel. The numerous experimental studies of Haden and Orr contributed materially to a better understanding of the chemical changes attending obstruction of the upper part of the intestine. Investigations concerning the causes of death in obstruction of the bowel have not proved especially fruitful. A number of facts have been learned, but many things remain to be explained.

It is now known that the elevation of blood urea, decrease in plasma chlorides and increased combining power of the blood for carbon dioxide obtain with regularity only in high intestinal obstructions, but not sufficiently early enough to be of diagnostic value. Saline solution acts like a specific in high obstructions only, and not as an antidote or detoxifying agent, but as a substitute for important fluids lost by vomiting. The causes of death in low and midintestinal obstructions are not so well

1. Hartwell, J. A., and Hoguet, J. P.: Experimental Intestinal Obstruction in Dogs with Special Reference to Cause of Death and Treatment with Large Amounts of Normal Saline Solution. J. A. M. A. **59**:82 (July 13) 1912.

understood but appear in some degree to be correlated with the function of the different levels of the bowel.[2]

No concrete proof exists of the absorption of a toxin in intestinal obstruction foreign to the normal bowel. On the contrary, there are many bits of evidence that indicate that such abnormal absorption in the presence of an obstructed but viable bowel does not occur. It is to be freely conceded, however, that failure to demonstrate objectively such abnormal absorption does not constitute a complete denial of its occurrence. At the same time, however, it indicates that this is not the central tenet of the problem.

Surgeons have long known that a well performed enterostomy will save the majority of persons with late simple obstruction, but that an attack directly on the obstruction is extremely hazardous to the patient's life. Enterostomy is life-saving in such instances, not because it drains off a potent toxin that threatens the organism but because it relieves tension within the bowel, restores the normal blood supply, allows the continuance of absorption from the bowel (which practically ceases in obstruction) and permits the automatic establishment of the continuity of the bowel in the absence of a persistent intrinsic obstruction below.

Instances of strangulation obstruction in which the blood supply to the bowel is compromised present additional features beside the block in the bowel, viz., loss of blood incident to greater occlusion of the veins than of the arteries to the segment concerned and a bowel which will become nonviable with persistence of the strangulating mechanism. If the veins to a segment of bowel from 3 to 5 feet in length are tied off in the dog, the animal will die of hemorrhage (into the bowel) in from four to five hours. If an encirclement ligature is placed around the bowel and its mesentery, simulating more closely clinical types of strangulation obstruction, the animal will survive for about fifteen hours, and the loss of blood is shown to be an important item in its death. If the arteries alone are tied, the animal survives for about twenty hours. The loss of blood or blood plasma is minimal, the necrosis of the wall of the bowel being the signifiant item in terminating the dog's life (Scott and Wangensteen[3]).

2. Wangensteen, O. H., and Leven: Correlation of Function with Cause of Death Following Experimental Intestinal Obstruction at Varying Levels, Arch. Surg. **22**:658 (April) 1931, fig. 4.

3. Scott, H. G., and Wangensteen, O. H.: Studies in Strangulation Intestinal Obstruction: 1. Length of Life Following Various Types of Strangulation Obstruction in Dogs, Proc. Soc. Exper. Biol. & Med. **29**:424, 1932; 2. Blood Pressure Changes Correlated with Time, Length and Type of Intestinal Strangulation in Dogs, ibid. **29**:428, 1932; 3. Effect of Intravenous Injections of Peritoneal Fluids Recovered from Dogs Dying of Experimental Intestinal Strangulations, ibid. **29**:559, 1932; 4. Blood Losses in Experimental Intestinal Strangulations and Their Relationship to Degree of Shock and Death, ibid. **29**:748, 1932.

ESSENTIALS OF DIAGNOSIS

The importance of early recognition of abdominal disorders of an acute nature necessitating surgical intervention is generally recognized. A high degree of correlation exists between the ultimate mortality figure and the time intervening between the onset of the disaster and the institution of adequate treatment. Acute intestinal obstruction is no exception to this rule, and the persistently high mortality attending its surgical relief reflects only too plainly the effects of late diagnosis.

· In hospitals where the resident and attending staff alike are "obstruction minded," the supervention of acute intestinal obstruction during convalescence from operation is immediately recognized. The intern knows that the occurrence of crampy intermittent abdominal pain, which the patient is likely to term "gas pains," is identified as intestinal colic by the concomitant presence of loud intestinal borborygmi heard with the stethoscope at the acme of the pain. He knows that none of the other colics to which the abdomen is heir is characterized by the simultaneous occurrence of loud intestinal noises at the height of the cramp. After the establishment of the presence of intestinal colic, it only remains to determine whether the pain is due to mechanical obstruction, acute enterocolitis, a type of abdominal allergy or food poisoning, or to the presence of simple "belly-ache." On the basis of other evidence, such as the presence or absence of nausea and vomiting, diarrhea and intestinal distention, a reliable deduction can ordinarily be made.

An agent of great value in this interpretation is a single plate made of the abdomen with the patient supine. It reveals the presence of visible gas in the small intestine, a sign significant of intestinal stasis in the adult; it determines also the degree of distention of the bowel.

There are four causes commonly seen to contribute to delay in the diagnosis of acute intestinal obstruction:

1. Failure to appreciate that simple obstruction of the bowel is not accompanied by tenderness or rigidity of the abdominal wall.

2. Belief that the expulsion of gas or feces with an enema militates against obstruction of the bowel.

3. Assuaging of pain with morphine.

4. The deception of apparently effectual catharsis in partial obstructions.

Patients with strangulation types of obstruction almost invariably present local tenderness and rigidity of the abdominal wall due to the escape of hemorrhagic fluid into the peritoneal cavity. Their complaint and physical findings are otherwise those of intestinal colic as in simple obstruction. Patients with strangulation obstruction exhibit early slight quickening of the pulse incident to loss of blood into the infarcted segment, and early rises of fever to 100 and 101 F. are usual. There is no disturbance of the general condition of the patient early in simple obstruction. Chemical alterations in the blood occur with regularity only

in high obstructions and are usually not observed until forty-eight hours or more has elapsed following the onset of the obstruction. Leukocytosis may occur in either simple or strangulation obstruction incident to the dehydration of vomiting.

A patient complaining of intermittent crampy pain attended by nausea and vomiting without manifesting local tenderness or rigidity of the abdomen should be suspected of having simple intestinal obstruction. Should pain continue despite the effectual return of gas and feces with enemas in the presence of visible distention of the small intestine, on roentgen examination the diagnosis of intestinal stasis can reasonably be made. The occurrence of loud intestinal borborygmi significant of

Fig. 1.—Roentgenogram of the abdomen of a patient with "functional spastic ileus." The distention is limited to the colon. This patient had been operated on six times previously for acute intestinal obstruction.

increased peristaltic activity of the bowel at the height of the pain establishes the stasis as being mechanical in nature. The stethoscope is an important agent in the diagnosis.

Elsewhere [4] I have described a group of cases in which no organic obstruction is present which simulate the clinical picture of acute mechanical obstruction very closely. The gaseous distention, however, is confined entirely to the colon and the stomach. The history and the gaseous distention as visualized on the x-ray film (fig. 1) serve to identify the

4. Wangensteen, O. H.: Elaboration of Criteria upon Which the Early Diagnosis of Acute Intestinal Obstruction May Be Made, with Special Consideration of the Value of X-Ray Evidence, Radiology **17**:44 (July) 1931.

Fig. 2.—Roentgenogram showing distention of the colon due to carcinoma of the sigmoid flexure. There was no distention of the small intestine, owing to the competence of the ileocecal sphincter. At operation the cecum was found to be gangrenous due to the tension.

Fig. 3.—Roentgenogram showing incomplete adhesive obstruction of the small intestine. Gas is present in the colon, but the latter is not distended. Decompression was effected by suction siphonage through a nasal catheter.

condition. The roentgen features of this condition resemble rather closely the colonic distention of carcinoma of the sigmoid flexure with obstruction (fig. 2). Partial adhesive obstructions in which gas is already present in the colon (fig. 3) are not to be mistaken for this variety of functional spastic ileus. The gaseous distention of the small intestine differentiates the two.

REMEDIAL AGENTS

Early release of the obstruction is the keynote of successful therapy of acute intestinal obstruction. In the majority of instances, immediate recourse is to be had to surgical measures of relief. Strangulation varieties of intestinal obstruction are always to be dealt with surgically as quickly as possible because of the threatened devitalization of the obstructed bowel. Some types of simple obstruction, especially those in which decompression of the bowel (enterostomy) serves to reestablish its continuity, can be satisfactorily treated by nonoperative means (suction siphonage by nasal catheter).

Saline Solution.—This solution exhibits the virtues of a specific only in high obstructions. Clinically, the only types which are indisputably known to be "high" are those at the pyloric outlet of the stomach and those which occasionally obtain temporarily at the stoma after the performance of gastro-enterostomy or gastric resection with anastomosis (Polya). In such instances, the surgeon feels safe in observing expectant treatment, replacing the fluid lost from the stomach by the generous administration of saline solution. In all obstructions, adequate administration of fluid is important, but the widespread impression that saline solution rehabilitates patients with acute intestinal obstruction is to be corrected. Though salt and water are important agents in combating the dehydration incident to persistent vomiting from obstruction, they do not accomplish miracles. Release of tension by decompression of the bowel in simple obstruction and early release of the constricting mechanism in strangulation obstruction are the ends to be attained.

During the hour that preparations are being made in the operating room, physiologic solution of sodium chloride should be freely administered (from 2 to 3 liters) by the intravenous and subcutaneous routes. In those instances in which the roentgenographic film indicates that the degree of intestinal distention is not great, more time may be consumed to replace adequately the fluid lost by vomiting.

Blood Transfusion.—For the poor surgical risk, transfusion is always a great boon. In simple obstruction, the transfusion of blood, just as the generous use of saline solution, fortifies the patient in some measure for the ordeal that he must undergo. Only in strangulation

types of obstruction, in which the loss of blood is frequently a significant item, is transfusion urgently indicated. In any patient with this type of obstruction presenting a high pulse rate and low blood pressure, transfusion is to be performed before operation. The adequate replacement of the blood lost is also important. The shock features of strangulating varieties of obstruction are synonymous with loss of blood, and shock in the healthy adult at any rate is not precipitated by lesser losses of blood than from 800 to 1,000 cc. In the ill patient, lesser losses are probably more telling. Nevertheless, transfusions for blood lost must be adequate.

Recently an infant of 18 months was observed at the University Hospital with an intussusception of about fifty hours' duration. The pulse was weak and extremely rapid, the rate being about 200. There was no manifest improvement after the subcutaneous and intravenous infusion of 700 cc. of saline solution. After the transfusion of 250 cc. of blood, the patient's condition improved remarkably. The pulse fell to 160, and reduction of a compound intussusception (entero-enteric and ileo colic) together with excision of a Meckel's diverticulum at the apex of the intussusception was accomplished without event, the patient making a satisfactory convalescence.

Suction Siphonage by Nasal Catheter.[5]—I have long employed conservative means in dealing with instances of functional spastic ileus, previously described, but was first led to employ drainage by suction in the treatment of acute mechanical obstruction in the following case:

E. J., a woman, aged 72, was admitted to the hospital with an obstruction of seventy-two hours' duration, and operation obviously was danger. The systolic blood pressure was 80 mm. of mercury, and the patient was badly dehydrated. Past experience with cases of this sort had taught that saline solution alone, even when administered for some considerable period of time, did not improve the patient materially as a surgical risk. The details of the apparatus and the manner of its employment are shown in the accompanying sketch (fig. 4).

The roentgen film (fig. 5 *A*) showed that considerable distention of the entire small intestine was present. It was felt that if a lessening of the distention could be accomplished the risk of the operation could be definitely decreased. After the insertion of the nasal catheter and the commencement of suction, the crampy pain of which the patient complained ceased at once. After eight hours' suction (fig. 5 *B*), during which time 200 cc. of fluid and 800 cc. of gas were aspirated, the distention of the small intestine was considerably reduced and the patient's condition was equally improved. After forty hours' suction, there was complete disappearance of gaseous distention (fig. 5 *C*). Because of the conjectured persistent nature of the obstruction (thought to be carcinoma of the cecum), operation was done. A stricture of the terminal ileum, probably syphilitic in nature, was

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5. Wangensteen, O. H.: The Early Diagnosis of Acute Intestinal Obstruction with Comments on Pathology and Treatment with a Report of a Successful Decompression of Three Cases of Mechanical Bowel Obstruction by Nasal Catheter Suction Siphonage, West. J. Surg. **40**:1 (Jan.) 1932; Tr. West. S. A., 1931.
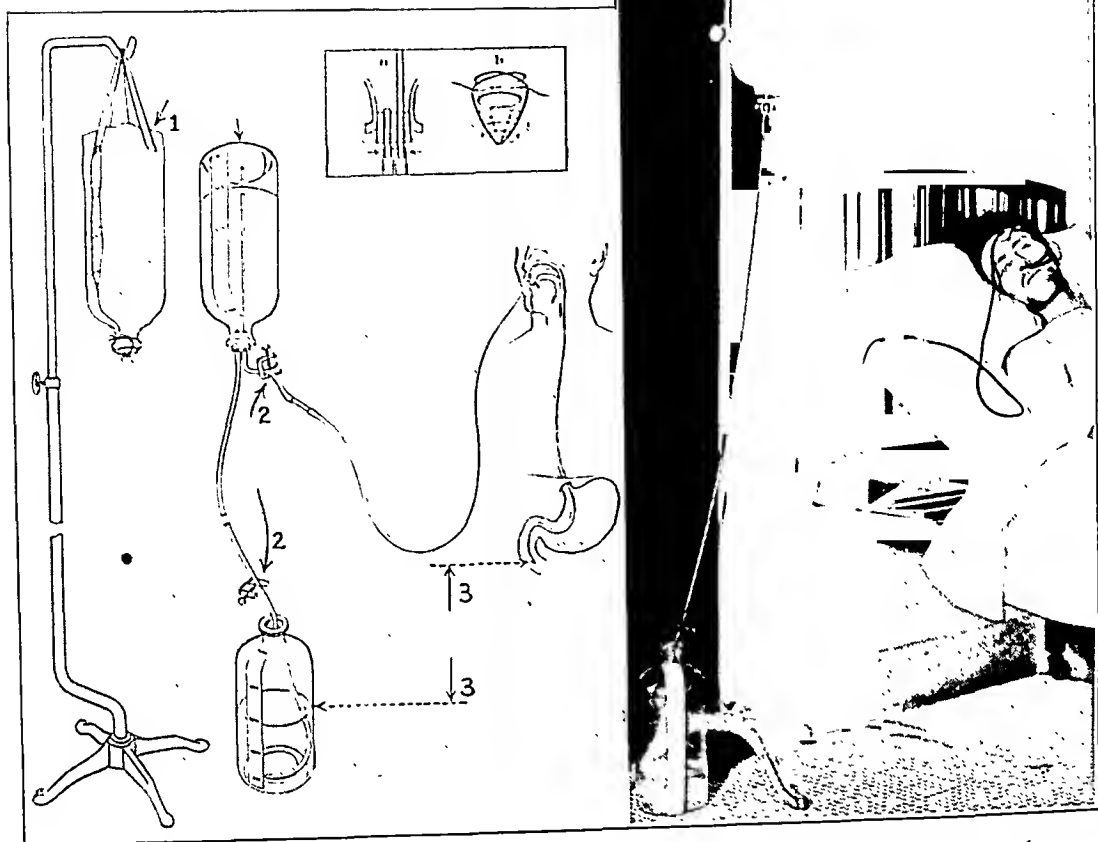
Fig. 4.—Sketch of the apparatus employed for suction siphonage through a nasal catheter, and a photograph of the apparatus in use. In the sketch, *1* indicates the canvas holder for the upper bottle; *2*, the clamp, to be used when the nasal tube is removed or the lower bottle emptied; *3*, the vertical distance—the degree of negative pressure in the nasal tube varying directly with this distance (2 feet, 6 inches has been found satisfactory—(*a*) to the lower bottle and (*b*) to the patient.

Fig. 5.—Roentgenograms of the abdomen of Mrs. E. J., 72 years old. *A* was taken on admission to the hospital with seventy-two hours' acute obstruction. The entire small intestine is distended. *B* was taken after eight hours' suction with a nasal catheter, during which time 200 cc. of fluid and 800 cc. of gas were aspirated. *C* was taken after forty hours' suction, showing complete decompression.

found.[6] The stricture was divided in the longitudinal axis of the bowel, the strictured area was invaginated into the cecum and a proximal enterostomy was done, following which the patient convalesced uneventfully.

Since then, successful decompression without operation has been done on seven patients with acute adhesive obstruction.

L. F., a boy, aged 9 years, was admitted to the hospital on Oct. 13, 1931. He had been operated on three years previously at the University Hospital for acute suppurative appendicitis with peritonitis. On his admission with acute obstruction, he gave a history of vomiting and intermittent colicky pain of forty-eight hours' duration. There was no rebound tenderness or abdominal rigidity. The roentgen film (fig. 6 A) showed considerable distention of the upper part of the intestine. Immediately after the institution of suction the pain stopped, and a film taken three hours later (fig. 6 B), at which time 550 cc. of fluid and 650 cc. of gas had been aspirated, showed complete disappearance of the gaseous distention of the small intestine. After twenty hours' suction (fig. 6 C), no gaseous shadows were visible in the abdomen. Since the institution of suction, 1,625 cc. of fluid and 2,250 cc.

Fig. 6.—Roentgenograms of the abdomen of L. F., 9 years old. A was taken on admission to the hospital with a forty-eight hours' acute obstruction. B was taken after three hours' suction, when 550 cc. of fluid and 650 cc. of gas had been aspirated. C was taken twenty hours after commencement of suction; 1,625 cc. of fluid and 2,250 cc. of gas were aspirated meanwhile.

of gas had been recovered by aspiration. The suction was then discontinued, and the patient was permitted water by mouth, followed by clear liquids, and gradually solid food was allowed. He was permitted to be up and about, but it was felt that since he had previously had lesser attacks of the same sort the obstructive mechanism should be sought out and freed. Fifteen days after his admission, laparotomy was performed and an obstructive band in the midportion of the small intestine was found acutely angulating the bowel and binding it down to the root of the mesentery. The band was divided and the bowel released; the patient was dismissed from the hospital fourteen days later.

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6. Strictures of the lower portion of the small bowel behave peculiarly occasionally. I have recently observed an instance of intermittent obstruction of a subacute nature due to a stricture of the terminal ileum that would not admit the little finger. Still the patient was well without obstructive features for long intervals.

Successful decompression with suction siphonage by a nasal catheter without subsequent operation on the obstructive mechanism has been done in five patients with acute adhesive obstruction.

Mr. C., aged 26, presented acute adhesive obstruction seven days after an appendectomy for acute suppurative appendicitis. Enemas proved ineffectual in relieving his pain. Immediately after starting the suction, he had relief from pain After seventy-two hours' suction, the bowel was completely decompressed and water was permitted by mouth.[7] The patient was subsequently discharged well.

Mr. B., aged 41, was admitted to the hospital with acute intestinal obstruction after having been successfully operated on elsewhere for the relief of acute obstruction about a month previously. The obstruction was only partial as shown by the persistent presence of gas in the colon. Suction siphonage by nasal catheter alone sufficed to decompress the bowel, and the patient was dismissed with the instruction that should he continue to have attacks of pain and vomiting it would be wise to establish the uninterrupted continuity of the bowel by severing the adhesive constricting bands at operation.

After the performance of enterostomy for the relief of adhesive obstruction, it is rarely necessary to have to deal later with the obstructive mechanism. Despite its persistent presence, just as mysteriously as the obstruction was initiated, so after effectual decompression the intestinal current goes on uninterrupted, and the patient suffers no ill effects from the continued presence of the adhesive bands. In the presence of universal adhesions causing continuous pain or intermittent obstruction, it is necessary to free the bowel at an opportune time.

Somewhat more than a year ago I did the thirty-first operation for a girl who had been operated on thirty times previously for obstruction of the bowel and fistula. The entire bowel was freed, from the duodenojejunal angle to the cecum, and on completion of the operation air was injected into the peritoneal cavity. The patient's sacrum was kept elevated with three pillows so that the air would accumulate beneath the anterior abdominal wall, chiefly about the umbilicus, and mechanically separate bowel and anterior abdominal wall during the healing phase. This patient has remained quite well without pain or complaint referable to the bowel. except for the occurrence of slight vomiting during a recent attack of salpingitis of the fallopian tubes. Air injected in this manner is not likely to be of any value in the prevention of interintestinal adhesions. The patient's own serum (defibrinated blood) should prove to be fully as efficacious as, and have some distinct advantages over, amniotic fluid for this purpose.

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7. In the use of suction with the nasal catheter after abdominal operations, patients are permitted to drink clear fluids freely from the start. When an actual mechanical block exists in the bowel, however, it has been thought wise to deny the patient fluid by mouth until the intestinal distention is gone. A more accurate estimate of the fluid and gas removed is also obtained by this precaution.

Miss G. R. was admitted to the University hospital on March 20, 1932, with an acute intestinal obstruction three months after operation for acute suppurative appendicitis elsewhere. At the time her appendix was removed it had been necessary for her to remain in the hospital four weeks because of profuse drainage from her wound. On her admission to the University Hospital, twenty-four hours after the onset of vomiting, she complained of intermittent cramplike pain occurring at frequent intervals. There was no abdominal tenderness, and the abdominal wound was healed. Stethoscopic examination revealed loud intestinal noises at the acme of the pain, establishing the presence of intestinal colic. Rectal examination disclosed a small tender mass in the pelvis (culdesac abscess). A film of the abdomen (fig. 3) showed moderate distention of several coils of small intestine. The presence of gas in the colon following expulsion of gas with previous enemas which had been administered on admission indicated that the obstruction was incomplete. An administered Noble's enema [7a] was returned with some flatus but no relief of pain, and suction by nasal catheter was instituted. There was immediate cessation of pain after the insertion of the catheter, and the tube quickly found its way into the duodenum, as shown by a subsequent plate. The decompression progressed satisfactorily, and after two days' suction the gaseous shadows were scarcely visible on the x-ray film. On the third day the catheter was clamped occasionally, and clear liquid was permitted by mouth. Suction through the nasal catheter was continued intermittently until the fifth day after admission, since which time there had been no recurrence of pain.

During the first night (twelve hours), 900 cc. of fluid and 200 cc. of gas were aspirated through the nasal catheter. In the next twenty-four hours, 800 cc. of fluid and 600 cc. of gas were obtained with the nasal catheter and 1,950 cc. of gas and 50 cc. of fluid by the rectal suction. In the following twenty-four hour period, 450 cc. of fluid and 800 cc. of gas were aspirated by the nasal catheter and 100 cc. of gas and no fluid by a rectal tube similarly connected with a suction apparatus. A Noble's enema was given with effectual results and rectal suction was discontinued. In the following twenty-four hours, 1,200 cc. of fluid and 900 cc. of gas were obtained by the nasal catheter and in the last twenty-four hour period before suction was abandoned, 400 cc. of fluid and 700 cc. of gas were removed.

The worth of decompression by nasal suction was recently put to a severe test in the instance of a man of 35 in whom acute intestinal obstruction developed fourteen days after operation for suppurative appendicitis.

A. W., aged 35, had complained of intermittent "gas pains" for about thirty hours before vomiting occurred. Attempts at obtaining expulsion of gas with enemas had proved ineffectual. A diagnosis of acute intestinal obstruction was not established until vomiting took place. At this time (Feb. 26, 1932, 1:45 a. m.) considerable distention of several coils of small intestine in the left half of the abdomen was apparent on the x-ray film (fig. 7 A). Suction siphonage by nasal catheter was started at once with immediate cessation of cramps, and after a few hours the patient declared himself to be comfortable and stated that he had never felt better in his life. An expression that he frequently repeated during the period that the suction was employed was, "I feel like a million dollars."

Bedside films were made again at 2 p. m. and 11 p. m. (fig. 7 B). These showed the stomach emptied, but only a slight diminution in intestinal distention had occurred. On the evening of February 26, the suction was increased to about 250

7a. Noble's enema: turpentine, 1 drachm (3.75 cc.); glycerin, 2 ounces (59.2 cc); magnesium sulphate, 3 ounces (89 cc.); water, 4 ounces (118.4 cc.).

cm. of water (the nasal suction employed being 75 cm.), but when the film was made at 11 o'clock, it was not noted that the distal end of the catheter had returned into the lower end of the esophagus. This was not noted until 7 a. m. on February 27. Only 700 cc. of gas and 800 cc. of fluid had been aspirated since the institution of suction.

The tube was pulled out again and reinserted and apparently soon made its way into the duodenum; the decompression of the distended bowel progressed nicely, as shown in a film made at 9 p. m. on February 27 (fig. 7 C). When the drainage of gas and fluid was computed at 6 a. m. on February 28, it was found that 1,100 cc. of gas and 1,900 cc. of fluid had been aspirated during the preceding twenty-four hours. An x-ray film taken at 8 a. m. showed the small intestine to be absolutely decompressed, no gaseous distention being present. At 10:00 a. m., the suction was discontinued by clamping the tube, and 1,250 cc. of clear strained liquids was allowed by mouth. At 6:30 p. m. an enema was given, following which some flatus was expelled. At 7:00 p. m. another bedside film was taken (fig. 7 D). Gas was noted in the colon for the first time since the diagnosis of obstruction had been made, indicating that the continuity of the bowel was being reestablished. Incident to the allowance of oral fluids and temporary discontinuance of suction, however, gas had again accumulated in the small intestine. At 8:15 p. m. suction was commenced again. Suction was also applied to a rectal tube, and during the night 100 cc. of gas and 100 cc. of fluid were aspirated by the nasal tube and 100 cc. of gas and no fluid by the rectal tube.

An x-ray film taken at 8:00 a. m. on February 29 showed much less gas in the bowel than twelve hours before, and clear fluids were again permitted by mouth. About 10:00 a. m. it was noted that gas began to collect rapidly in the bottle connected with the rectal tube. When the computation was made at 6:00 a. m. on March 1, it was noted that the following drainage had occurred in the preceding twenty-four hour period: by nasal catheter, 1,800 cc. gas and 2,810 cc. fluid; by rectal tube, 7,700 cc. gas and no fluid. Suction was continued intermittently through March 1, and by March 2, the patient was passing gas freely by rectum and complained of being extremely hungry. Nasal suction was discontinued, and fluid and solid food were permitted by mouth. The continuity of the intestinal lumen remained patent despite the administration of food, and it was manifest that there had been complete recovery from the obstruction of the bowel.

In the last few days of the period of intestinal obstruction it was apparent that a small culdesac abscess was forming. The patient evacuated mucus several times a day by rectum without expelling gas or feces. Following the discontinuance of rectal suction, several warm enemas a day were given, and by the time that the patient was ready to be up no trace of the abscess could be made out on digital examination of the rectum. There has been no recurrence of "gas pains" since dismissal from the hospital.

Though the decompression of the distended small bowel progressed fairly rapidly in this instance, it was the appearance of gas in the colon (fig. 7 D) that afforded encouragement in knowing that the obstruction had been overcome. Visualization of gas in the colon in complete obstructions is synonymous with the reestablishment of the intestinal current and has in a manner the same significance for patient and physician as the exultation and delight experienced by a shipwrecked mariner on the sight of another sail.
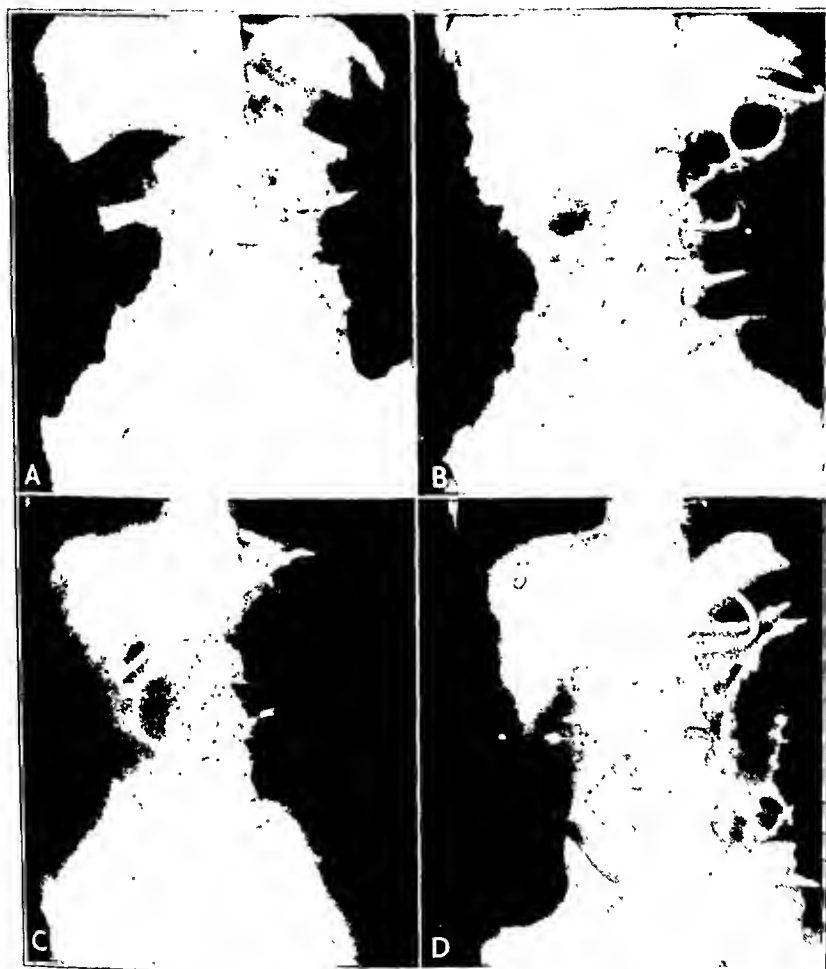
Fig. 7.—Roentgenograms of the abdomen of Mr. A. W., 35 years old. *A* was taken fourteen days after operation for acute suppurative appendicitis. There is considerable distention of the stomach and the small intestine. *B* was taken at 2 p. m., thirteen hours after the institution of suction. The stomach is empty, but there has not been much reduction of the distended coils of the small intestine. *C* was taken forty-four hours after suction was started. An effectual reduction in distention of the small intestine is present, but practically no gas has progressed into the colon. *D* was taken twenty-two hours later. There is now considerable gas in the colon, heralding the establishment of the continuity of the intestine.

Mr. J. E., aged 50, was admitted to the hospital on April 7, 1932, complaining of intermittent crampy pain, nausea and vomiting, of forty hours' duration. On admission paroxysms of pain occurred at intervals of from five to ten minutes, and loud intestinal borborygmi were heard with the stethoscope at the acme of the pain. The patient had also noted the concomitant occurrence of noise and pain. There was slight but definite tenderness of the abdominal wall, most easily demonstrated as rebound tenderness. One month previously the patient had a lesser attack of pain accompanied by nausea and vomiting from which he spontaneously recovered. He had had no previous abdominal operation. For ten years he has had a right inguinal hernia and has worn a truss for five years. The hernia has not recently been incarcerated. X-ray films of the abdomen revealed considerable distention of the upper coils of small intestine. Gas and feces were evacuated with enemas, but the pain still continued.

The slight tenderness and rigidity present here indicated that there had been an escape of fluid into the peritoneal cavity, suggesting the presence of a potential strangulation mechanism. As the pulse and temperature were not appreciably elevated, I thought that one might proceed cautiously with suction, watching the patient carefully for signs of increasing tenderness. Suction by nasal catheter was started at midnight on April 7. There was also immediate relief of pain, though the tenderness was still definitely demonstrable. On April 8, at 6 a. m., 800 cc. of gas and 600 cc. of fluid had been aspirated. There was not much reduction in the intestinal distention, as shown in the x-ray film. An enema was given during the night without effect. Two capsules of amyl nitrite were broken in some gauze for the patient to inhale, and he was turned on his right side. Some time later the tube made its way into the duodenum, and the suction became more effective. During the next twenty-four hours (April 9 at 6 a. m.), 1,700 cc. of gas and 900 cc. of fluid were aspirated, and an x-ray film of the abdomen showed definite reduction in distention, though the upper jejunal coils were still somewhat dilated. During sleep at 1 a. m., April 10, the patient pulled the catheter out. A Rehfuss tube was then put down through the mouth. No reliable measurement of gas could be made for the preceding twenty-four hours because of the extraction of the tube by the patient. An x-ray film made on April 10 at 8 a. m. showed almost complete disappearance of gaseous distention of the jejunum, and gas was present in the colon.

Clear fluids were permitted in small amounts by mouth, and the catheter was occasionally clamped. Suction was discontinued on April 12, and a roentgenogram taken on April 13, following a barium sulphate meal, showed the motor transit of barium through the bowel to be normal. The patient was allowed to be up and about, but wished to have his hernia repaired, which was done on April 25. Because of the antecedent obstruction, a low rectus incision was made permitting of examination of the abdominal contents as well as repair of the sac from within. A long strand of omentum was found to be engaged and adherent in the mouth of the hernial sac. It was delivered, and the hernial opening was closed. About 3 feet proximal to the cecum, there was an area about 2 inches in length where the small intestine presented a circular, thickened, opaque whitish plaque, representing undoubtedly the site at which the obstruction had occurred. The patient convalesced uneventfully and was dismissed on May 4.

R. B., a boy, aged 8 years, was seen in consultation at the Norwegian Deaconess Hospital with Dr. Frank Anderson, through whose courtesy I am permitted to include this case report. This patient had been admitted on Feb. 26, 1932, complaining of pain, nausea and vomiting. A diagnosis of intussusception was made.

and at operation an enteric intussusception of about 6 inches in length was reduced. The postoperative convalescence was uneventful, and the patient was dismissed on March 11.

On March 18, he was readmitted because of recurrence of his complaint. At operation a reinvagination of the small intestine was found to have occurred. Reduction could not be effected, and the bowel was of questioned viability. Resection was therefore done, and an end-to-end anastomosis made. There was gradual improvement until March 22, when the patient began to complain of abdominal cramps, followed by nausea and vomiting, and these were the complaints at the time I saw the boy on the evening of April 4.

Intermittent colic occurred periodically, and coincident with the pain loud intestinal borborygmi could be heard with the stethoscope. There was moderate distention of the abdomen, which was tympanitic above and somewhat dull immediately below the umbilicus, where the margins of the wound were indurated. The remainder of the abdomen was rather soft, though slight rebound tenderness could be elicited. From the indurated portion of the wound a fecal-smelling exudate could be expressed (colon infection, not feces). An x-ray plate made of the abdomen showed moderate distention of the small intestine. The button used for anastomosis was seen to be in the region of the ileocecal valve.

Suction siphonage by nasal catheter was instituted with immediate relief of pain and distress. Para-oral fluids were freely administered. During the next forty-eight hours, 1,500 cc. of gas and 1,460 cc. of fluid were aspirated. Some gas was evacuated by rectum, and the patient was permitted a little water and clear fluid by mouth, the tube being clamped occasionally. During the next twenty-four hours, 500 cc. of gas and 300 cc. of fluid were aspirated, and in the following twenty-four hour interval, 600 cc. of gas and 200 cc. of fluid; the button was expelled on April 9. The suction was continued intermittently for the next three days, approximately 600 cc. of gas and 300 cc. of fluid being aspirated each day. The patient was discharged well on April 18.

Mr. B. V., a hemophiliac, aged 23, was admitted to the hospital on May 7, 1932, because of abdominal pain, nausea and vomiting. The pain had commenced on May 3; on May 4 it increased, and in the evening he vomited. He continued to take liquid food, but on May 5, the pain, nausea and vomiting were greatly exaggerated. On May 6, following a dose of salts, a small tarry stool was passed; the pains became more severe, and the vomiting which was previously bilious became brown.

His physician, Dr. C. Roholt of Waverly, Minn., saw the patient at this time and observed tenderness in the lower left quadrant of the abdomen as well as a tender oblong mass at the same site. On May 7, there was tenderness in both lower quadrants. An enema returned a bloody stool. The vomiting was persistent and frequent, and borborygmi were audible to the unaided ear at the acme of the pain.

The patient had previously been admitted to the University Hospital because of a hemorrhage into the knee joint following slight trauma and a spontaneous hemorrhage into the right eye in January, 1930. The patient has suffered from prolonged bleeding since infancy. One brother died in infancy of hemorrhage from a slight cut in the tongue. A maternal uncle has hemophilia. On examination the patient was found to be blind in the right eye. The blood pressure was 134 systolic and 88 diastolic. The hemoglobin was 72 per cent and the white blood cells, 14,190. The clotting time was two hours and twenty minutes. The urine contained considerable albumin as well as many red blood cells, hyaline and granular casts. There was moderate distention of the abdomen with slight tenderness

and rigidity of the entire abdomen, more marked below. At the height of the intermittent pains which recurred periodically, intestinal borborygmi were plainly audible. An x-ray film taken of the abdomen showed considerable distention of the upper loops of jejunum. A slight amount of gas appeared to be present in the colon.

A diagnosis of hematoma in the bowel and mesentery causing mechanical obstruction was made and suction was instituted, liberal amounts of fluid being given para-orally. Considerable bloody fluid was evacuated from the stomach at first. On the morning of May 8, the patient felt much better; 2,200 cc. of gas and 1,000 cc. of fluid had been aspirated during the previous night. Two hundred units of theelin were given by the medical staff, and twenty minutes later the coagulation time was five minutes. An x-ray film made at 1 p. m. on May 8 showed marked reduction in the intestinal distention. Gas was evacuated by rectum. On May 9, the patient appeared much improved and had no complaints. Only 400 cc. of gas and 300 cc. of fluid having been aspirated in the previous twenty-four hour period, suction was discontinued and the patient was permitted fluid by mouth. The clotting time at 2 p. m. was twenty minutes. Fifty units of theelin was given on May 10, the obstruction having cleared up. The patient was transferred to the medical service for continuance of the treatment of hemophilia and has since been dismissed.

Suction by nasal catheter alone proved unsuccessful in the case of a boy of 16 years convalescing from an operation for acute suppurative appendicitis.

J., aged 16, was admitted to the hospital on Oct. 28, 1931, for an appendectomy. On the fourth day after operation symptoms of obstruction developed. Pain continued despite effectual evacuations with enemas, and suction was instituted. Pain ceased at once, but successive roentgenograms (fig. 8 *A* and *B*) made at an interval of twelve hours failed to show any appreciable decrease in intestinal distention. An unsuccessful attempt was made to pass the nasal tube into the duodenum under the fluoroscope in this case, it being felt that spasm of the pylorus was probably responsible for the failure. Enterostomy was then done, following which a decrease in the intestinal distention and progress of gas into the colon became apparent (fig. 8 *C*). The patient was discharged well thirty days after admission.

This was the third case in which suction had been employed in the treatment of acute intestinal obstruction, and in the first two instances the decompression progressed rapidly. I was a bit dismayed by the persistence of the distention in the small intestine and felt that enterostomy, an operation of established value, should take precedence over this unorthodox procedure of emptying the bowel. The patient was comfortable from the time that suction was started. however. With the experience gained in similar stubborn instances, previously related, I should now have tried somewhat longer before having recourse to enterostomy. In the rather limited experience which opportunity has afforded for trial of the method. I am inclined to believe that in practically all instances of obstruction of the small bowel decompression can be done by this method if the tube can be gotten through the pylorus when decompression cannot be performed with the catheter in the

stomach.[7b] In those instances, however, in which the obstructive mechanism does not relent, resort must be had to operation as the following case will illustrate.

R. E., a boy, aged 8 years, was admitted to the University Hospital on March 20, 1932, with a diagnosis of acute appendicitis. The symptoms were of seventy-two hours' duration. The temperature on admission was 102 F., and the pulse was 110. The white blood cells were 23,850, 90 per cent of which were polymorphonuclears. There were diffuse abdominal tenderness and rigidity. No masses were palpated by rectum, though the tenderness was marked.

A diagnosis of diffuse peritonitis of appendical origin was made, and the conservative plan of treatment which had been employed in such instances was carried out, viz., massive hot packs to the abdomen, para-oral fluids and suction by nasal catheter to relieve distention. The patient had a fairly stormy time, but gradually improved and appeared to do well after March 29.
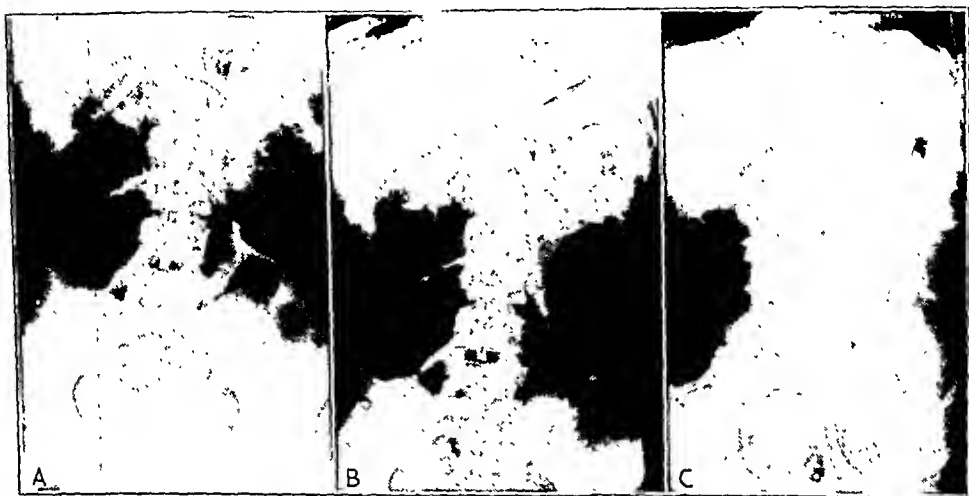
Fig. 8.—Roentgenograms of the abdomen of a boy, aged 16. *A* shows acute obstruction which developed four days after appendectomy. *B* was taken after suction siphonage by nasal catheter had been employed twelve hours; there is no appreciable reduction in distention; *C* was taken twelve hours after enterostomy; gas is present in the colon and the distention of the small intestine is considerably diminished.

On April 23, at which time the patient appeared to be otherwise quite well, intermittent pain occurred. Gas was expelled with enemas, but the pain continued. On the morning of April 24 the cramps were severe, and loud borborygmi were

7b. It was soon learned that it is an important item in accomplishing decompression with the duodenal catheter to have holes cut back on the tube for about 10 inches (25.4 cm.), so that constant suction may be exerted in the stomach as well as in the upper reaches of the small intestine after the tip of the catheter has gone beyond the pylorus. The details of technic of decompression have been described by Dr. J. R. Paine and myself elsewhere (Nasal Catheter Suction Siphonage: Its Uses and the Technic of Its Employment, Minnesota Med. **16**:96 (Feb.) 1933.

audible with the stethoscope at the acme of the pain. Considerable distention was present, and when vomiting occurred at 2 p. m., a roentgenogram was made of the abdomen which showed considerable distention of both large and small bowel to be present (fig. 9 *A*). Masses of feces are visible in the ascending colon on the film. Though lumps of hard feces were expelled with enemas, the pain continued.

A diagnosis of partial obstruction was made (gas in colon), and suction by nasal catheter was commenced; pain stopped at once. Fluid was interdicted by mouth, but was administered intravenously. A roentgenogram made at 9 : 30 p. m. showed some decrease in distention of the upper coils of the small intestine; 3,625 cc. of gas and 150 cc. of fluid had been aspirated in the meantime. An x-ray film made at 10 : 30 a. m. on April 25 showed considerable reduction in the gaseous distention of the small intestine with almost complete evacuation of the gas in the colon (fig. 9 *B*). An abscess on the external aspect of the right thigh containing considerable greenish pus (staphylococcus) was opened at this time. On April 26, the patient was permitted fluid by mouth, the catheter being clamped periodically.

Fig. 9.—Roentgenograms of the abdomen of a boy, aged 8 years. *A* shows acute obstruction; about five weeks previously he was admitted to the hospital with diffuse peritonitis of appendical origin which subsided under conservative treatment. *B* was taken twenty hours after instituting suction. (The obstruction developed again after appendectomy, and the bowel was again decompressed by suction siphonage with a nasal catheter, but when feeding was started gaseous distention recurred necessitating enterostomy. Later, release of the constricting agent also became necessary.)

On April 27, the suction was discontinued, and the patient continued to do well. On the afternoon of April 29, pain was complained of in the right lower quadrant, and there was definite rebound tenderness. An x-ray film showed some return of gaseous distention of the small intestine. Suction was recommenced and carried through the night. The next morning, appendectomy and drainage of an appendical abscess was done. The patient had already been ill for more than a month, and transfusions had meanwhile been given. Nasal suction was continued intermittently for three days after operation. By May 3, the patient was doing very well, taking solid food and exhibiting daily improvement. On May 8, feces made their

appearance in the wound (fistula at site of removal of appendix), but there were no complaints, however. On May 10, the patient again complained of abdominal pain attended by borborygmi, and there was emesis of 200 cc. The abdomen was distended, and enemas gave no relief. An x-ray film demonstrated considerable distention of the small intestine.

Suction was begun with relief of pain and reduction of the distention, as visualized on the x-ray film. The nutritional problem in this child who had been ill for seven weeks was now a significant consideration. Every attempt to feed him, however, resulted in an increase of the intestinal distention. An enterostomy was done under local infiltration anesthesia on May 16 without reaction. At operation strands of fibrin were visible over the coils of bowel, undoubtedly a residual of the diffuse peritonitis for which the patient was admitted. Suction was subsequently applied to the catheter in the bowel. By May 18 there was no distention, and the patient declared himself to be hungry and began to take solid food. A few days later symptoms of obstruction developed again despite the·fact that the enterostomy tube was draining freely. A direct attack [8] was then made on the obstructing mechanism near the site of appendectomy, and a catheter was inserted into the fistulous opening in the cecum. The patient has been improving but will probably need an operative procedure to close the fistulous opening in the cecum persisting after appendectomy.[8a]

Satisfactory decompression was obtained following the first attack of obstruction of the bowel in this child. Shortly after appendectomy and drainage of an appendical abscess, obstruction recurred. The small bowel could again be satisfactorily decompressed, but attempts at feeding resulted in increased distention, indicating the necessity for enterostomy. Later release of the persistent obstruction bands also became necessary.

This series of eleven cases in which decompression was achieved by suction through a nasal catheter (enterostomy was also done in two) is marred through death in one case (Mr. O. N., aged 52), for which the method is in no way to blame. A successful decompression of the small intestine was obtained by suction, but the obstruction continued. Because of the long continuance of the obstruction and the weakened condition of the patient, repeated efforts were made to interrupt the suction and allow liquid nourishment orally. Following each attempt the small bowel distended again, and operation was undertaken. Whereas, ordinarily in such cases I have done enterostomy as a routine measure, in this instance, because of the preliminary decompression and because of an unwarranted interest as to the nature of the obstruction (my impression was carcinoma of the small intestine), I took the liberty of locating its site. A small mass was found in the terminal ileum, apparently confirming the impression of carcinoma. A gentle attempt was made to elevate the mass. and directly an escape of fecal material into the wound from the mass was observed; the patient's fate was sealed by this unhappy maneuver. The leakage was mopped up, the

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8. In a fairly large number of enterostomies which I have performed this is the second instance in which a subsequent operation on the site of obstruction was necessary in order to establish the continuity of the intestine.

8a. The fistulous opening in the cecum has since been closed, and the patient in a recent letter declared himself to be entirely well.

tiny opening in the bowel closed and a proximal enterostomy done, but
these were futile corrective measures in the presence of this spillage,
and the patient died of peritonitis seven days later.

The patient's history anterior to operation was briefly as follows:

About eight weeks before entry to the hospital the patient was seized with
abdominal pain followed by hiccup and frequent vomiting. There had been blood
in the stool and a loss of 30 pounds (13.6 Kg.) in weight. On examination the
patient was found to be much dehydrated and showed evidence of considerable
recent loss of weight. Visible and palpable peristalsis was present, and loud
intestinal borborygmi were audible synchronous with the crampy pains of which
the patient complained. The blood urea was 51 mg. per hundred cubic centimeters;
blood chlorides, 395 mg., and the result of the Van Slyke test was 76 per cent by
volume. The hemoglobin was 108 per cent. Moderate distention of the small
intestine, especially in the left portion of the abdomen, was present on the x-ray
film. Suction siphonage by nasal catheter was continued for the next three days
before the bowel showed disappearance of the gaseous shadow in the small intes-
tine. Each attempt at interrupting suction in order to feed the patient orally
resulted in increasing distention. On the sixth day after admission, because of the
conjectured nature of the obstruction, operation was done; 11,050 cc. of fluid and
4,800 cc. of gas had been aspirated during the interval.

Postmortem examination failed to disclose the cause of the obstruction. The
most logical explanation would appear to be that a foreign body (not discovered
at operation or autopsy) perforated the bowel and gave rise to an inflammatory
mass, the manipulation of which caused the leakage.

Simple enterostomy would have obviated this unhappy issue. Unfor-
tunately, however, too often, an error committed cannot at once be
undone and another plan projected without accepting some penalty from
the indiscretion. Experience in surgery would command no special value
could one, as in O. Henry's "Roads of Destiny," on following out
unsuccessfully one course of action start on another untrammeled and
with peace of mind and without handicap seize on another mode of
attack. A lesson taught here should be that the safest procedure is the
most conservative. Suppression of curiosity as to the nature of the
obstruction would have saved this patient's life and me considerable
embarrassment.

Suction siphonage by nasal catheter has its shortcomings and is not
to be recommended in the treatment of strangulation obstruction, which
is to be recognized clinically in the occurrence of rebound tenderness.[9]
In carcinoma of the sigmoid flexure in which gaseous distention involv-
ing only the colon usually obtains, due to competence of the proximal
ileocecal valve, drainage of the upper reaches of the bowel by catheter
would be inadequate; and when the cause continues to operate, as in

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9. Doubt may be entertained by some as to whether simple and strangulation
obstructions can be differentiated without operation. In any borderline case cer-
tainly operation is to be done, but I feel definitely as set forth elsewhere (Northwest
Med. **30**:389 [Sept.] 1931) that the physical findings will serve to distinguish
these varieties.

the instance of the first patient previously referred to, it is not to be expected that drainage through a nasal catheter alone will suffice. In adhesive types of obstruction in which the cause usually ceases to operate following decompression of the bowel, the method should have its greatest usefulness, and in postoperative obstruction particularly the method should prove to be an agent of therapeutic value. In the use of the method it is wise to follow the intestinal decompression by taking frequent x-ray films of the abdomen (portable) until it is obviously apparent, from the degree of intestinal distention present, whether the method will be successful or not.

It is extremely important that enough fluid be administered by the subcutaneous and intravenous routes during the time that suction is in force to insure a good daily urinary output (about 1,000 cc.). If the distention subsides satisfactorily and a liberal urinary output obtains, it is not necessary to follow the chemical changes in the blood. Except in unusual instances the daily output of urine is as reliable an index of whether enough fluid and salt are given as are frequent determinations of the blood chlorides, urea and carbon dioxide-combining power of the blood. In the cases referred to in this paper, from 4,000 to 6,000 cc. of fluid has been given daily. With the removal of fluid from the stomach and upper reaches of the bowel it is imperative to give considerably more fluid than the ordinary patient requires. Physiologic solution of sodium chloride is usually given subcutaneously on the outer aspects of the thigh beneath the fascia lata and 10 per cent dextrose solution (sometimes in physiologic solution of sodium chloride) intravenously.

Measures to assuage pain have been unnecessary. With the institution of suction the pain almost invariably miraculously ceases. An occasional lesser cramp is sometimes complained of. In the latter cases in this group, most of them instances of recent postoperative obstruction following surgical intervention for suppurative conditions, I have employed hot packs to the abdomen as a routine measure. This helps to relax the abdominal muscles and is worth while.

With the oral source for increase in the gaseous distention shut off by suction, even in those instances in which the decompression of the distended bowel has progressed slowly, it has been remarkable how the patient's condition, as well as his comfort, improved incident to the interruption of accretion in distention. Borborygmi may be made out with the stethoscope, but they are not as violent and as frequent as before. When the bowel has become accommodated to a certain grade of distention, if no tendency toward progression is exhibited, the peristaltic activity apparently lessens. A few of the patients have complained a little about the presence of the tube in the throat, but the instillation of a few drops of nasal oil has usually mitigated this distress.

In a few patients the end of the tube persisted in the stomach throughout, and a satisfactory evacuation of the small bowel was

obtained.   Where the decompression has progressed rather slowly, I
have been anxious to see the catheter make its way beyond the pyloric
sphincter into the duodenum.   In one instance (an early case), previ-
ously listed, the decompression failed because it was impossible to get
the catheter into the duodenum.   In two subsequent cases, the inhalation
of amyl nitrite appeared to facilitate the entry of the catheter into the
duodenum.

There is one distinct advantage that enterostomy presents over
decompression by means of suction through a nasal catheter, viz., the
opportunity to feed the patient as soon as the decompression has been
effected.   In complete types of simple obstruction it may take some
time for the continuity of the bowel to become reestablished, as heralded
by the appearance of gas in the colon despite complete disappearance
of the distention.   Fortunately, in most instances, successful decom-
pression is followed quickly by automatic reestablishment of the con-
tinuity of the bowel, but in those in which an interval obtains between
these events, attempts at feeding without an enterostomy usually result
in a renewal of the distention.

The rationale of the success of this method in decompressing the
bowel undoubtedly resides in the fact that the chief source of the
gaseous distention is swallowed air.   When the decompression is estab-
lished by enterostomy, there is frequently little escape of gas or fluid
after the initial release of the catheter.   The escape of some gas and
fluid permits the angulation or kinking of the bowel to become adjusted
and righted, and the continuity of the intestinal current becomes auto-
matically established.   This explanation no doubt holds true in some
measure of the decompression effected by nasal suction.   The removal
of intestinal gas through the nasal catheter decreases the distention of
the obstructed bowel and permits the gas to go down into the lower
reaches of the bowel.

All persons with simple acute mechanical intestinal obstruction
observed at the University Hospital since August, 1931, when the
method was first successfully employed, with the exception of three
with carcinoma of the sigmoid flexure, which, as previously stated,
constitutes a contraindication to its use, have been treated by suction
siphonage through the nasal catheter.   During this interval (until
May 1, 1932) only twelve such patients have been seen, all of whom are
referred to in this report.   Decompression was unsuccessful in an early
case by this method because the catheter did not enter the duodenum.
In another, decompression was successfully effected by suction but
recurred sixteen days later.   The distention of the small intestine was
again satisfactorily dealt with by suction by nasal catheter, but attempts
at feeding the child who had been ill for more than seven weeks resulted
in increasing distention.   Enterostomy was done to permit of feeding.
In nine instances a satisfactory decompression was obtained by suction

alone. In another, also decompressed by suction, in which the obstruction continued, the patient unfortunately died following an ill advised attempt to ascertain the nature of the obstruction and reestablish the continuity of the bowel.

The method has also been successfully used in a fairly large number of instances of subacute and chronic obstructions not enumerated in this report, due chiefly to narrowing of the pelvic colon and rectum by carcinoma of the pelvic genital organs of the female. Through relief of the obstruction by nasal and rectal suction in such instances and subsequent regulation of the diet and administration of liquid petrolatum, many such patients have been spared a terminal colostomy. Suction by nasal catheter has been employed also as an auxiliary aid in the relief of distention following the release of strangulation obstructions (hernias and intussusceptions).

NOTE.—At the time of proof-reading this paper, twenty-four cases of acute mechanical obstruction of the small intestine have come under observation since suction siphonage by nasal catheter was first employed in the treatment of mechanical obstruction. Decompression has been done in twenty of these by suction siphonage through nasal catheter alone. In four instances enterostomy also became necessary. In the entire group there have been two deaths (8.3 per cent): the one referred to in the text of this paper and another, the case record of which will be briefly reviewed. Mrs. H., aged 66, was admitted to the University Hospital on Aug. 10, 1932, for disease of the gallbladder following a severe attack of a few weeks previously. In addition to a well developed acute intestinal obstruction, the cause of which was a packet of gallstones resembling the cast of a gallbladder impacted in the ileum, she had a large infected bed sore over the sacrum, with considerable fever. Suction siphonage by nasal catheter was instituted, and the gaseous distention of the small bowel disappeared. Owing to her generally poor condition, feeding was attempted through the catheter, and alternate feeding and suction proved successful despite the continued presence of the gallstones in the small intestine. Six weeks later signs of acute intestinal obstruction again developed. Pituitary extract was unfortunately given; perforation of the intestine occurred, and the patient died of peritonitis a few days later. A timely operation in the unobstructed phase would perhaps have avoided this disaster.

A questionnaire has been submitted to the patients treated in this manner, and the majority state that they have no complaints referable to the intestinal canal. This material together with other details of treatment will be made the subject of a subsequent report.

OPERATION

Elsewhere [10] I have described in some detail the conduct of the operative procedure in acute intestinal obstruction. Here the principles of operation will alone be briefly outlined.

Anesthesia.—In patients with early intestinal obstruction the choice of the anesthetic agent is not a matter of paramount importance. Patients with late obstruction exhibiting considerable regurgitant vomit-

10. Wangensteen, O. H.: The Diagnosis and Treatment of Acute Intestinal Obstruction, Northwest Med. **30**:389 (Sept.) 1931.

ing are poor risks for an inhalation anesthetic because of the danger of aspiration. I have used spinal anesthesia almost entirely, with complete satisfaction. In postoperative obstructions, local infiltration is usually adequate. In infants, local infiltration reenforced by a small amount of ether serves the purpose well.

Incision.—When the type and location of the obstruction remain undetermined, a subumbilical midline incision is best made. Care must be taken that the urinary bladder at operation is empty, especially following the generous preoperative administration of fluid. In the relief of postoperative adhesive obstruction by enterostomy, a small oblique incision opposite the umbilicus over the outer edge of the left rectus muscle has been made as a routine procedure.

Choice of Procedure.—In the operative relief of simple obstruction the surgeon should permit himself to be guided solely by the general condition of the patient. In early cases, the operation of election can be done, viz., locating the exact site of obstruction, determining its nature and releasing the block that obstructed the bowel. In late cases, enterostomy, an operation of necessity, is much the safer procedure. All anastomotic procedures on the dilated intestine are to be deliberately avoided.[11] In strangulation obstruction, the condition of the bowel after its release and not the patient's general condition must determine the choice of procedure. No matter how ill the patient, if nonviable bowel is present, it must be excised. Exteriorization with the establishment of complete external fistula followed by a secondary anastomosis carries a much lesser risk to the patient's life than excision and primary anastomosis.

Enterostomy.—Site: The nearer the enterostomy is to the point of obstruction, the more efficient is the drainage. A deliberate attempt to make a "high" enterostomy is to be avoided. I have observed that the amount of drainage (gas and fluid) is correlated only with the degree of obstruction present, and not with the level at which the enterostomy is done.

Technic: A distended coil of bowel is seized and drawn out through the wound. Should the bowel present with any difficulty, the incision should be adequately enlarged to avoid injury to the serous coat of the distended intestine. Before placing a single stitch in the distended wall of the bowel, it is highly essential that the segment selected be emptied of its content. This may be done by milking it out between the fingers and isolating the collapsed segment between clamps; or if the wall of the bowel is too tense, the rubber-covered clamps should be first applied and the distended segment aspirated with a long fine needle and a large syringe.

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11. Congenital intestinal atresia is an exception to this rule, the only reported recoveries having occurred after an entero-anastomosis. Infants do not tolerate fistula of the small intestine.

Immediately following emptying of the thin dilated bowel, the circular muscle of the intestine contracts and the wall of the bowel presents a surprising increase in thickness, rendering suture of the bowel a safe procedure and precluding leakage from the stitch holes which would otherwise occur. Removal of the content from the segment on which enterostomy is to be performed also does away with all danger of the slightest spillage on introduction of the catheter into the bowel.

In the performance of enterostomy for acute intestinal obstruction, there must be absolutely no spillage. The slightest soiling invites peritonitis and is synonymous with failure. The needles and suture material should be fine (chromic catgut 000 or silk). A urethral catheter, no. 14 French, is scored as shown in the accompanying diagram (fig. 10) and a fine 000 chromic catgut ligature is fixed in the groove. The catheter is then buried in the wall of the bowel by the Witzel technic, the suture starting about 1½ inches proximal to the scoring on the catheter. The proximal end of the catheter must always be clamped off before the bowel is punctured. A Bard-Parker blade no. 11 or a fine cataract knife is used for the puncture. The distal end of the catheter is pushed into the lumen of the bowel, and the enfolding stitch is continued for another 1½ inches. An aseptic enterostomy can be done in this manner (fig. 11), the most important feature in establishing an effectual decompression with minimal risk.

The segment on which enterostomy has been performed can be safely dropped back into the peritoneal cavity without the slightest fear of leakage. Omentum need not be sought to cover it.[12] When the catheter comes away about the tenth to twelfth day (unless adhesive fixation on the skin continues to retain it), the tiny peritoneal tunnel closes spontaneously without subsequent leakage. Persistent fistula after removal of the catheter is due to employment of too large a catheter or to the use of the multiple purse string suture which angulates the bowel and obstructs it. A no. 14 catheter will drain the bowel as well as a garden hose.

Exteriorization.—The time factor and the rigidity of the constricting agent are the significant items in determining whether a strangulated bowel will be found to be nonviable. Whereas many types of obstruction of the bowel are potentially instances of strangulation obstruction from the beginning, primary thrombosis or embolism of the mesenteric vessels is the only type of strangulation in which excision of the devitalized bowel is mandatory. In all other potential strangulations, release of the obstruction before the anatomic changes consequent on prolonged interference with the blood supply of the segment have occurred obviates the necessity of dealing with a nonviable bowel. A fine balance of judgment must occasionally be exercised in dealing with a questionably viable bowel in a patient in poor condition. Should the decision be made to leave it, the nutrition of the segment should be protected by making a proximal enterostomy to prevent distention, or the same effect can be insured by the use of suction siphonage by nasal catheter after operation. Bowel that is frankly nonviable should be excised. A resection with immediate anastomosis is to be deliberately avoided. Even though

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12. When performing enterostomy for postoperative obstruction, one rarely finds omentum available, the inflammatory focus having previously attracted it.
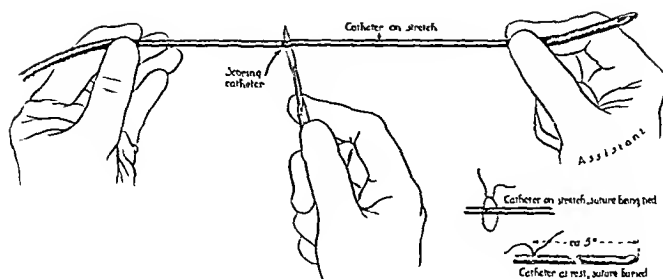
Fig. 10.—Method of scoring catheter to fix it in the bowel.
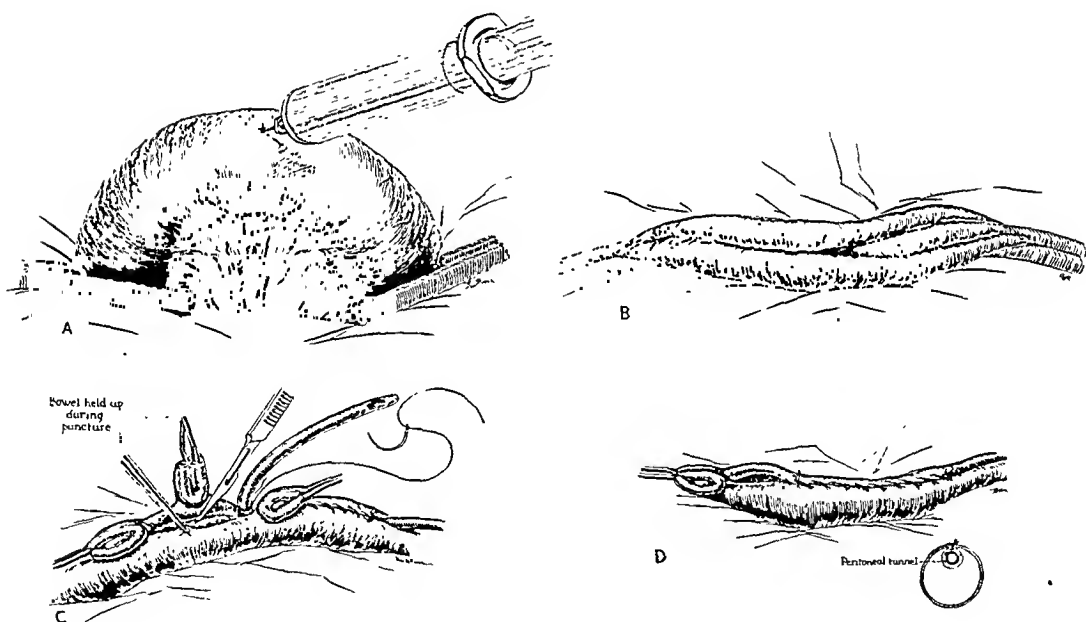
Fig. 11.—Technic of enterostomy: *A* shows the emptying of an isolated loop of its content to permit of an aseptic enterostomy. Usually the greater content can be "milked out" between the fingers. The loop should be completely evacuated with an aspirating needle, however, before any sutures are placed. *B* shows the condition of a much dilated and thinned out intestinal wall immediately after aspiration. *C*, a no. 14 (French) urethral catheter is laid on the bowel and a running stitch of 000 chromic catgut enfolds the bowel about it over a length of 1½ inches; a tiny puncture is made and the catheter introduced into the lumen; the fixation stitch (scoring) is placed and the peritoneal tunnel is continued for another 1½ inches. *D*, the suture is completed; the insert shows the peritoneal tunnel within the bowel in which the catheter lies.

generous lengths of intestine on either side of the devitalized segment are simultaneously removed, the danger of subsequent death from peritonitis is great.

Only under unusual circumstances, such as gangrene of the greater length of the small bowel, is a primary anastomosis to be done. The prohibitive mortality of doing a resection with anastomosis in the presence of devitalized bowel is well illustrated in strangulated external hernias. At the Friedrichshain Hospital in Berlin between the years 1903 and 1922, 1,795 persons with strangulated external hernias were treated, of whom 280, or 15.6 per cent, died. In 1,509 cases without gangrene there were 136 deaths (9 per cent); of the 286 persons
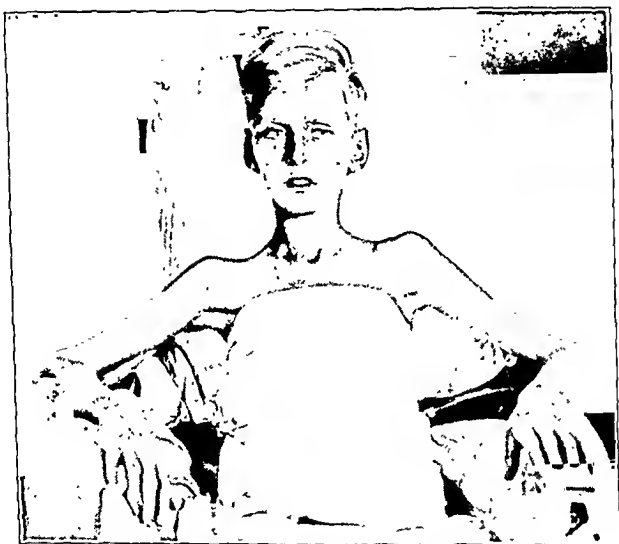
Fig. 12.—Exteriorization of the bowel when nonviable in strangulation obstructions. The gangerenous bowel is cut off after the skin is closed and catheters are tied into each loop. The continuity of the bowel is restored by a secondary anastomotic procedure.

with gangrene necessitating resection 144, or 50.4 per cent, died! Frankau recently reported the results of a collective investigation instigated by the Association of Surgeons of Great Britain and Ireland on strangulated hernia. The mortality for the group was 15.7 per cent. In 105 instances, because of gangrene of the bowel, resection was done, with 45 deaths, a mortality of 42.8 per cent.

The devitalized segment should be brought out through the incision,[13] and on completion of the skin closure, the dead bowel is to be cut off

13. In strangulated external hernia, when the patient's condition permits, the hernia should be repaired after exteriorizing the intestine through a separate short midline incision.

and a catheter tied into each loop (fig. 12). By this means the intestinal content escaping through the proximal catheter may be collected and allowed to run into the distal loop by the gravity drip method. After about six to eight days, it becomes difficult to keep the catheter in the proximal loop satisfactorily, and a secondary anastomosis should be done as soon as the patient's condition will permit. Children particularly do not tolerate well the presence of a high fistula. Its persistence for some time without satisfactory replacement of the escape from the proximal loop into the distal will result in a severe nutritional disturbance that may prove difficult to combat.

SUMMARY AND CONCLUSIONS

Early recognition of acute intestinal obstruction is of paramount importance in treatment. A block in the continuity of the bowel is best identified by establishing the presence of intestinal colic, viz., the audition of loud intestinal noises with the stethoscope at the acme of intermittent crampy pain.

All instances of strangulation obstruction are to be subjected to immediate operation. When nonviable bowel is found, it is far safer to exteriorize the devitalized segment and establish the continuity of the bowel secondarily than to effect a primary anastomosis after resection.

In many patients with acute simple intestinal obstruction decompression can be performed by suction siphonage with a nasal catheter. Instances of adhesive obstruction are particularly amenable to relief by this method. Many patients with late simple obstruction (intrinsic) in which the cause continues to operate can be improved as operative risks by preliminary decompression with the duodenal tube and suction. Inspection of roentgen films of the abdomen is the best criterion in determining whether the decompression is progressing satisfactorily. Of twelve patients with acute simple obstruction observed since the method was first used, successful decompression has been obtained in nine; one of these had a stricture in the terminal ileum, another was a hemophiliac in whom the obstruction was due to hematoma in the bowel. The obstruction in the other seven instances was of adhesive nature, in three cases of remote origin and in four recent. In two of the three instances in which drainage by catheter was not successful enterostomy was done, though in one of these satisfactory decompression was obtained with suction alone. The other patient died following an attempt to relieve the obstructive mechanism and to reestablish the continuity of the bowel. Decompression has also been employed successfully in several instances of subacute and chronic obstructions and as an auxiliary agent after the operative relief of strangulation obstructions. In obstructions of the left half of the colon (usually carcinoma) with

ballooning of the proximal colon with gas, the method is not recommended; in such instances cecostomy or appendicostomy should be done.

The operative treatment of acute intestinal obstruction is briefly discussed, and my method of performing enterostomy is described. Spillage or contamination during the operative manipulations is synonymous with failure!

The value of saline solution and transfusions of blood in the treatment of acute intestinal obstruction is reviewed. Saline solution exhibits the virtues of a specific only in high obstructions. In strangulation obstructions, loss of blood into the infarcted loop may be great, and the transfusion of blood is a great boon in aiding the recovery of patients so afflicted.

MECHANICS OF SCOLIOSIS

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The essential characteristics of the deformity observed in scoliosis have been understood for more than a hundred years. The voluminous literature of scoliosis deals largely with the cause or causes of the deformity, but mainly with the thousand and one methods which have been used in its treatment, with only a few serious studies of the mechanics involved. The striking similarity in the deformities resulting from such a variety of well established causes indicates a uniformity in the intermediate causes, that is, in the mechanics of the deformity. The purpose of this paper is to analyze the previous explanations of this mechanism and to add the results of some original investigations on mechanical models.

ANATOMIC CONSIDERATIONS

The spine is a segmented rod. Each segment consists of a body and a neural arch. The column of bodies is the weight-bearing element, weight bearing including the pressure stresses of all the muscles and ligaments tending to compress the spine. These muscles are attached to the bodies only through the medium of the neural arches.

The axis of all motions between contiguous vertebrae lies in the nucleus of the disk, as may be demonstrated by a careful study of roentgenograms, and as illustrated in Morris' "Human Anatomy." [1] The intervertebral joints are rudimentary diarthrodial, as stated by Smith.[2] Motions allowed are tilting in all planes and rotation. Motion in any one joint is sharply limited by ligaments and articular processes, but the type is double ball and socket, the nucleus pulposus acting as a ball-bearing between adjacent bodies. Use of the term "universal joint" is to be condemned because a universal joint, as the term is used in mechanical engineering, does not allow rotation.

The range of motion allowed in the intervertebral joints is in all directions from the anatomic position of the spine with the normal anteroposterior curves present. The normal anteroposterior curves are therefore no safeguard against lateral deformity.

1. Jackson, C. M.: Morris' Human Anatomy, ed. 8, Philadelphia, P. Blakiston's Son & Co., 1925, p. 536.

2. Smith, N. R.: The Intervertebral Discs, Brit. J. Surg. 18:358, 1931.

TYPE OF DEFORMITY

The term "rotary lateral curvature" indicates the two elements of deformity commonly recognized. Lateral curves are labeled right or left to indicate the side of the convexity. In the presence of a primary curve to one side, secondary curves develop which tend to bring the two ends of the spine back into the same planes and preserve general bodily alinement.

Rotation is an integral part of side bending. The bodies rotate toward the convexity of each curve, so that the lateral deviations of the column of bodies are greater than the deviations of the spinous processes. Rotation is greatest at the apex of each curve and tends to be greater in the primary than in compensatory curves. The degree of rotation observed frequently exceeds by far the degree allowed in a normal spine. In the lumbar spine, where normal rotation is almost nil, rotation of 45 degrees frequently occurs, the observations of Calvé[3] to the contrary notwithstanding. As in paralytic clubfoot the tarsal bones grow into a shape allowing more and more deformity, so in the spine the maintenance of a position at one extreme of normal range of motion causes young bone to adapt itself to greater and greater degree of deformity. Each isolated vertebra is stated to rotate about a point in space about 1 inch (2.5 cm.) posterior to the tip of its spinous process. As regards the whole column, however, each vertebra rotates on its adjacent vertebra about a long axis passing through the nuclei of the disks.

A third element of deformity has been observed with sufficient frequency in paralytic and idiopathic cases to warrant consideration. This is kyphosis. In the dorsal region it appears as an increase in the normal kyphosis and in the lumbar as a decrease in the normal lordosis or as actual kyphosis. Like rotation it tends to be greatest in the primary curve and like lateral curvature it tends to be compensated for by the anteroposterior curve above or below. Several authors have pointed out that the apparent kyphosis in a dorsal curve is partly due to prominence of the transverse processes and ribs, but an actual kyphosis of the column of bodies through the primary curve, as shown in lateral roentgenograms, is the rule. Early stages of idiopathic scoliosis frequently show a simple exaggeration of the normal anteroposterior curves, that is, the picture of a relaxed or weak back. But as lateral curvature progresses, a relative kyphosis through the primary curve becomes apparent in the majority of cases. Some tracings of roentgenograms showing this factor are reproduced in figure 1.

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3. Calvé, J.: Some Preliminary Observations on Scoliosis, Am. J. Orthop. Surg. **12**:13, 1914.

MECHANICS OF PRODUCTION

A number of explanations of the mechanics of the deformity have been advanced from time to time. Some of them are conflicting. Their multiplicity in itself urges a critical review.

1. *Inequality of Columns.*—Historically after Dods,[4] whose observations were incorrect, comes the explanation of Meyer,[5] followed by Bauer [6] and lately mentioned by MacLennan.[7] Meyer based his theory on two important observations: that strong ligaments existed, anterior and posterior, but not lateral, to the vertebral bodies, and that the column of bodies was compressible while the column of laminae was elastic. MacLennan mentioned unequal growth of the two columns, but the principle is the same. In either case excess length of the column of bodies would cause, first, hyperextension of the spine. In the presence of lateral curvature, from habitual position or any other
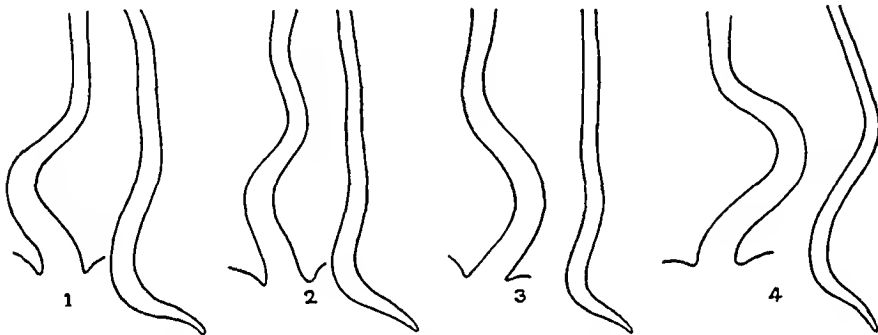
Fig. 1.—Tracings of columns of vertebral bodies from anteroposterior and lateral roentgenograms showing kyphosis, actual or relative, in the primary lateral curve.

cause, the too-long column of bodies would tend to digress from the midline farther than the column of laminae, especially with no lateral ligaments to prevent such deformity.

This ancient theory cannot be wholly denied. Objection to it can be raised on the ground that flexion and not extension is generally recognized as a prescoliotic stage, supported by Lovett's [8] conclusion

4. Dods, A.: Pathological Observations on the Rotated or Contorted Spine Commonly Called Lateral Curvature, London, Cadell, 1824.

5. Meyer, H.: Die Mechanik der Skoliose, Virchows Arch. f. path. Anat. **35**:125, 1866.

6. Bauer, L.: Lectures on Orthopedic Surgery Delivered at the Brooklyn Medical and Surgical Institute, ed. 2, New York, William Wood & Company, 1882.

7. MacLennan, A.: Scoliosis, Brit. M. J. **2**:864, 1922.

8. Lovett, R. W.: The Mechanics of Lateral Curvature of the Spine, Boston M. & S. J. **142**:622 (July 14) 1900.

that rotation first occurs in positions of flexion, and Abbott's [9] system of treatment in flexion. Mechanically, the theory has its undeniable points. It works out on the articulated spinal model. The transference of the anterior longitudinal ligament into a lateral position by rotation might serve to explain the spontaneous arrest of progress of deformity frequently observed. Lateral movement having been arrested in this manner, deformity could still progress in a direction lateral with respect to the rotated vertebrae or lateral and backward in relation to the trunk as a whole, which would be in line with clinical observation. I am inclined to think that this mechanism conspires with two others, one of which is responsible for starting the deformity in the same direction.

2. *Articular Facets.*—Adams [10] and Shaw [11] believed rotation due to changes in the posterior articular processes. Exception was taken to this a few years later by Judson [12] on the ground that rotation occurred early in the deformity while changes in the facets were seen only in late cases, and he concluded that such changes were secondary. It seems highly improbable that the facets could cause rotation in the direction in which it is observed. The lumbar facets allow almost no rotation, certainly favor none. The dorsal interarticular joint spaces form an arc with its center somewhere near the nucleus pulposus. But the surfaces lie in a plane passing upward and forward. If two dorsal vertebrae are taken, the upper tilted to the right on the lower and the interarticular facets kept in contact throughout the maneuver, the inferior facet on the right side of the upper vertebra will move downward and backward while that on the left will move upward and forward, producing rotation toward the right or concave side, a phenomenon opposite to that observed in scoliosis.

It must be concluded that the dorsal facets favor physiologic rotation of the entire trunk, as in turning to look behind, but serve only to limit the type of rotation associated with lateral deformity in scoliosis.

3. *Pressure of Ribs.*—No review of theories of rotation should omit the classic work of Feiss.[13] This author conceived the trunk as a hollow tube and argued as follows: Bending a tube to the side produces tension on the convex and laxity on the concave side. Tension

9. Abbott, E. G.: The Mechanics of a Plaster Corset in Lateral Curvature of the Spine. Am. J. Orthop. Surg. **12**:30, 1914.

10. Adams, W.: Lectures on the Pathology and Treatment of Lateral and Other Forms of Curvature of the Spine, ed. 2, London, J. Churchill & Sons, 1882.

11. Shaw, J., quoted by Adams [10] and Judson.[12]

12. Judson, A. B.: The Causes of Rotation in Lateral Curvature of the Spine, Tr. New York Acad. Med., April 6, 1876.

13. Feiss, H. O.: The Mechanics of Lateral Curvature, Am. J. Orthop. Surg. **4**:37 (July) 1906.

on the convex side pushes the ends of the ribs toward the concavity. The ends of the ribs push the posterior parts of the vertebrae toward the concavity, thereby rotating the anterior part or bodies toward the convexity. Feiss called this a retrograde or reactionary tendency. Some doubt is cast on this theory when it is remembered what a flexible member the rib is in a young child and more when one reflects how difficult it is to reverse the process, to reduce spinal rotation by pressing on the ribs. Lovett[8] held the opposite and more reasonable view when he said: "The ribs, of course, follow the rotation of the vertebrae to which they are attached." The classic case reported by Hoke[14] and recent reports by Sauerbruch[15] and Frey[16] indicate that pressure on the ribs may be used to correct a deformed spine, but it seems improbable that this method represents a reversal of the original mechanism.

4. *Mast and Stays.*—The spine, with its muscular and ligamentous support, has frequently been compared to a mast with its stays. The action of the transverse traction muscles, as described later in this paper, warrants this comparison. The analogy is dangerous only if used to cover all the mechanics of the spine.

5. *Bow and Strings.*—The spine has been compared to a bow. It has been argued that if a strung bow is pushed sidewise at its middle the bow will rotate rather than bend in a second plane. Of course it will, but the entire bow, the middle and both ends, will rotate, a phenomenon which bears no analogy to the scoliotic spine in which the ends remain in their original plane and rotation takes place through a limited area only and in the typical manner described. The spinal mechanism does partake of many qualities of a bow. The flexor muscles represent one long bow-string and the extensor muscles a series of short bow-strings. The significance of this difference will be discussed later. The analogy to bow-strings is satisfactory if used carefully.

6. *Child's Blocks.*—The most simple of all theories is that advanced by Dickson,[17] who said that the rotation reaction is similar to that which occurs if one takes eight or ten child's building blocks stacked one on top of the other in a column and, holding them in the two hands, brings pressure on them in such a manner as to exert more

14. Hoke, M.: A Study of a Case of Lateral Curvature of the Spine, Am. J. Orthop. Surg. **1**:2, 1903.

15. Sauerbruch, F.: The Surgical Treatment of Severe Scoliosis, Arch. f. klin. Chir. **118**:550, 1921.

16. Frey, R. K.: Surgical Treatment of Dorsal Scoliosis, Deutsche Ztschr. f Chir. **169**:13, 1922.

17. Dickson, F. D.: Operative Treatment of Lateral Curvature of the Spine, J. Missouri M. A. **24**:1, 1927.

force on one side than the other. When this is done the column bends and at the same time the individual blocks rotate on each other, this rotation being away from the side of greatest pressure and toward the side of least. This is exactly what vertebrae do when exposed to unequal pressure because of scoliosis. The only difficulty is that blocks do not behave in such a fashion. I have experimented with children's blocks for hours without being able to observe any such rotation. And I can see no reason to expect such a phenomenon.

7. *Flat Flexible Rods.*—The whole problem has been repeatedly dismissed with the magic formula "flexible rods." Both Dick [18] and Guérin [19] formulated a theory which was briefly stated by Bigelow [20] in 1844 as follows: "The principle of torsion rotation is illustrated by bending a blade of grass or a flat flexible stick in the direction of its width. The center rotates on its longitudinal axis to bend flatwise in the direction of its thickness." Smith [21] attacked this theory in 1931, pointing out that Bigelow's statement "implies that (1) there is continuity of substance in the spine, (2) the spine is flat, (3) the plane of flatness is in the frontal plane, (4) rotation is a concomitant element of lateral flexion." Smith attempted, however, to support the analogy of the "blade of grass" by including the idea of tripedal support, stating that "a cross section of the spine is not rectangular but triangular, with its greatest diameter in the antero-posterior plane. The amplitude is less in sagittal bending than in lateral bending. Any tendency to rotation is greater in sagittal than in frontal flexion."

The first two premises outlined by Smith are patently false. There is neither continuity nor flatness in a series of double ball and socket joints. There is an element of truth in the tripedal quality of the spine, whether the posterior points are represented by pressure between articular facets in extension or by tension of the capsules of these joints in flexion. The nucleus and the articular facets do form a triangle. But the side connecting the facets is the shortest side only in the lumbar and lower dorsal regions. In the upper dorsal and cervical regions this is the longest side, as may be seen from inspection of typical vertebrae from these regions (fig. 2). Yet rotation with scoliosis occurs in the same fashion in both regions.

In order to comprehend fully the "blade of grass" idea some experiments were performed with flat flexible rods. A strip of stiff card-

18. Dick, H.: A New Instrument for the Treatment of Spinal Curvature, M. Times & Gaz. 2:738 (Aug. 20) 1864.

19. Guérin, J.: Mémoire sur l'étiologie générale des déviations latérales à l'épine par rétraction musculaire active, Paris, au bureau de la Gaz. méd., 1840.

20. Bigelow, H.: Orthopedic Surgery, Boylston Prize Dissertation, 1844, Boston, W. D. Ticknor & Co., 1845, p. 168

21. Smith, L. D., in discussion of Carey.[26]

board 17 inches (43.1 cm.) long and five-eighths inch (1.6 cm.) wide was mounted in a vertical position with provision for lowering the upper end to allow bending. Both ends of the flat rod were mounted on universal joints to allow movement in two planes so regulated that the deviation of both ends from the vertical should be equal (fig. 3).
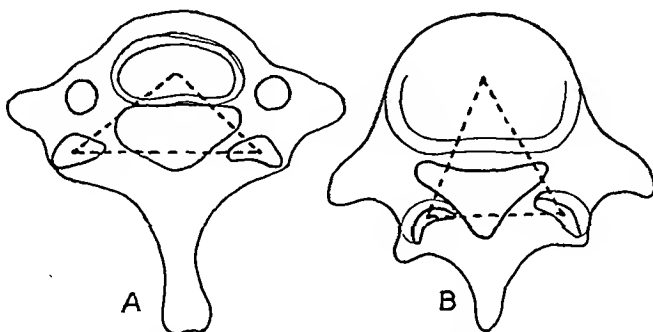
Fig. 2.—*A*, seventh cervical vertebra. *B*, fifth lumbar vertebra
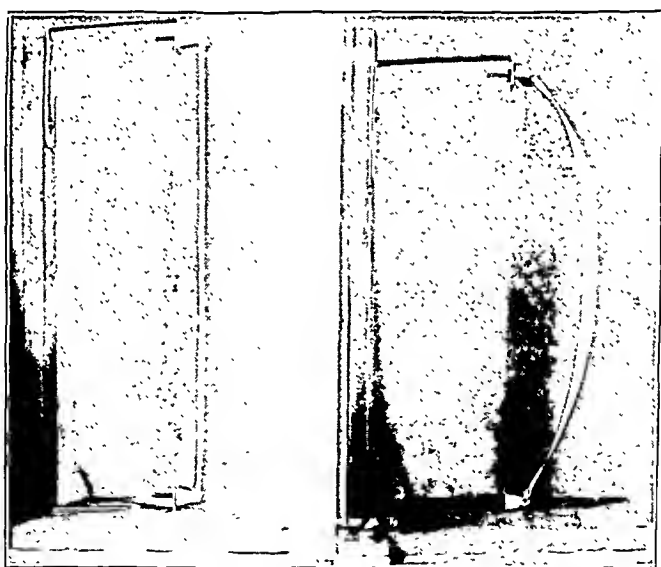
Fig. 3.—Rotation secured in an experiment with a flat flexible rod.

When the upper end was lowered, the cardboard bent in its thickness. When the joints above and below were set at 45 degrees in opposite directions to bend the cardboard in the diameter of its width, rotation took place in such a way that the concave edge bent farther out from the vertical in the plane of its thickness. Interpreted in terms of the spine this phenomenon is as follows: If the width of the cardboard be regarded as in the sagittal plane of the spine, kyphoscoliosis produces rotation of the anterior edge (bodies) to the convexity of the

lateral curve, as seen in clinical scoliosis. In lordoscoliosis the rotation is in the opposite direction. These two results, incidentally, are in accord with Lovett's [22] observations on movement in the normal spine. But to carry the analogy into the upper dorsal and cervical spine where the greatest diameter of the tripod is in the frontal plane, one must regard the width of the cardboard as representing the frontal plane of the spine. Here kyphoscoliosis produces rotation of the bodies toward the concavity of the lateral curve and lordoscoliosis produces rotation in the direction observed in clinical scoliosis. Yet in clinical scoliosis rotation is always that of bodies toward the convexity regardless of the level of the spine involved. The only conclusion possible from all this is that the spine bears no relation to a flat flexible rod, and that the "blade of grass" analogy is a poor one.

8. *Symmetrical Flexible Rods.*—As one of the conclusions from his notable research into the movements of the spine Lovett [8] stated: "The spine behaves in general as any flexible rod would under similar conditions so far as rotation is concerned."

Z. Adams [23] also said: "The column of bodies obeys the laws of flexible rods." The magic formula "laws of flexible rods" transfers the problem into the realm of applied physics, beyond the comprehension of busy surgeons. In my quest for such abstruse knowledge I sought the assistance of Dr. G. B. Pegram, head of the department of physics at Columbia University. Regarding the spine as a series of double ball and socket joints it may correctly be compared only to a symmetrical rod. A series of experiments was therefore inaugurated, using a thick-walled, small-bore, flexible rubber tube, and attempting to duplicate the conditions present in the spine.

The material used was Du Pont nitrometer tubing, an extremely flexible tube with an outside diameter of five-eighths inch and an inside diameter of one-fourth inch (0.6 cm.). In the first experiment a piece of tube 6 inches (15.2 cm.) long was mounted on a short dowel-pin in the center of a base ruled off with parallel lines (fig. 4). A scarf-pin was stuck through the tube near its upper end, horizontally and parallel with the base lines. A cotton thread looped about a common pin driven through the center of a small cork placed in the upper end of the tube provided a means of manipulating the tube without rotary stresses. Rotation of the tube was to be observed by looking down from above, noting the position of the scarf-pin in relation to the parallel base lines. The following results were noted: Pulling the tip

22. Lovett, R. W.: The Mechanism of the Normal Spine and Its Relation to Scoliosis, Boston M. & S. J. **5**:153, 1905.

23. Adams, Z.: The Relation of Bony Anomalies of the Lumbar and Sacral Spine to the Causes and Treatment of Scoliosis, Am. J. Orthop. Surg. **12**:45, 1914.

forward or backward in the plane of the indicator caused no rotation. Pulling the tip to either side, at right angles to the indicator, caused no rotation. Pulling the tip toward any intermediate point caused an apparent deviation from the parallel base lines when viewed from above. But it was also noted that in any such position the indicator was no longer horizontal to the base. This experiment, therefore, might be considered analogous to side bending of a normal spine, as the results agree in every way with Lovett's [22] observations, but not analogous to scoliosis.

It was thought that conditions of the spine could be represented more faithfully by a compound curve, keeping the two ends of the tube
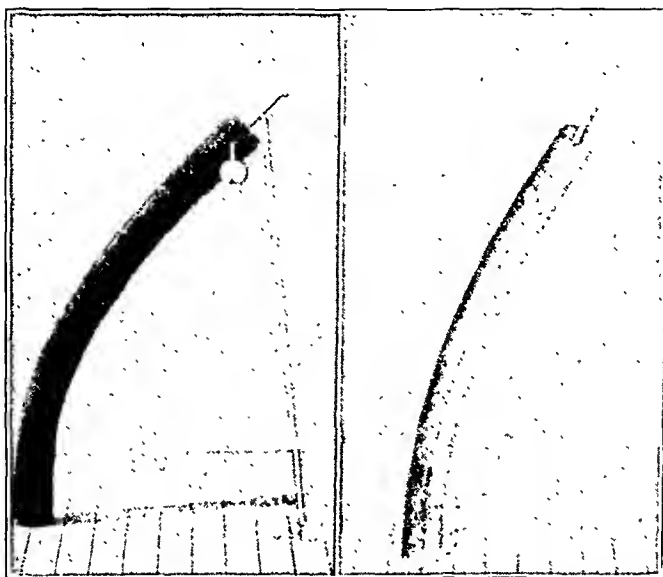
Fig. 4.—Experiment illustrating absence of rotation in a symmetrical flexible rod.

parallel and in the same plane, as they tend to remain in the scoliotic spine. A 17 inch piece of tubing was therefore mounted on a short dowel in the center of a base ruled off with parallel lines, and the upper end on a similar dowel beneath the cross-arm of a standard so arranged that lowering the cross-arm would produce a long curve in the center with compensatory curves near either end (fig. 5). A series of five scarf-pins were stuck through the tube at equidistant points, all parallel with each other and with the parallel lines on the base when viewed from above. The rod being perfectly symmetrical, the bulging of the tube from the vertical, caused by lowering the cross-bar, occurred with equal freedom toward any quadrant of the circle. The primary curve was rotated through the full circle by means of a wire loop passed

loosely about the midpoint of the tube in order to obviate any rotary stress. Looking downward from above, it was observed that throughout the maneuver the pins remained parallel to each other and to the base lines. This result is entirely in accord with the laws of physics. In a symmetrical rod there is no greater resistance to bending in one direction than another, and, therefore, no tendency to rotation.

This, then, disposes of the mystery of "flexible rods" as far as statics of the spine are concerned. A series of ball and socket joints can be compared only to a symmetrical flexible rod. And a symmetrical flexible rod does not rotate at all, either with side bending in extension
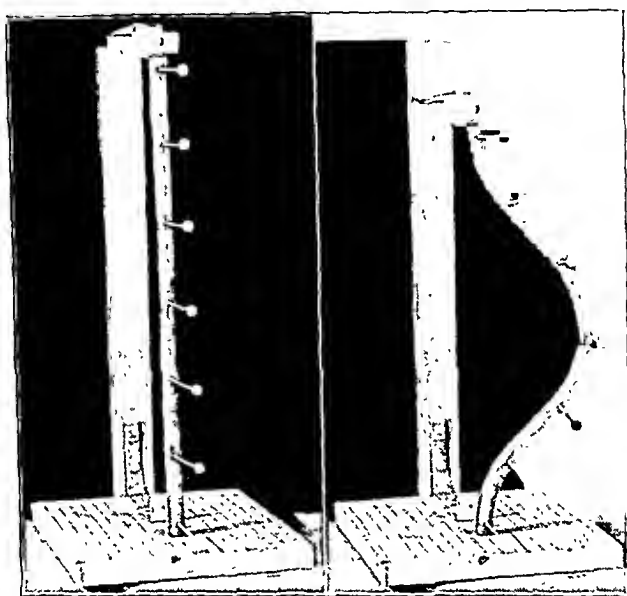
Fig. 5.—Another experiment with a symmetrical flexible rod, showing no rotation in a compound curve.

or with side bending in flexion. In considering the dynamics of the spine the flexible rod will be used again and a different story found.

9. *Muscle Imbalance.*—A. Action of Muscles: So far, I have considered only the static elements of the spine. Muscle is dynamic as compared to bone, cartilage and ligament, which are static. The form of bone, according to the laws of Wolff, which considered gravity only, or according to the remittent back pressure vectors of Carey,[24] which deal with muscle pull, is determined by the stresses placed on it. The static part played by ligaments is demonstrated by the way in which they stretch or shrink, as the need may be, to accommodate themselves

24. Carey, E. J.: Studies in Dynamics of Histogenesis. Radiology **13**:127, 1927.

to altered positions of the spine or of any other joint. Steindler[25] makes the excellent observation that "the ability of the spine to revert at will to perfect anatomic symmetry is the salient characteristic of normal function," and muscle is the only element subject to the will.

Muscles affecting the spine are many and their actions are complex. Several authors have attempted to classify them into more simple groups. Meyer,[26] in 1856, classified them into (1) posterior spinal, (2) anterior spinal (sternocleidomastoid and recti), (3) external oblique and intercostal, (4) internal oblique and intercostal and (5) transversalis. Judson,[12] in 1876, divided them into (1) those nearly parallel to the spine and (2) those connecting the vertebral column with the shoulders, the thoracic and abdominal parietes and the hips. Mackenzie[27] classified postspinal and prespinal muscles, the quadratus lumborum being the only prespinal muscle recognized in the dorsolumbar region. The latest classification, that of Carey,[28] recognizes (1) superficial parallel bow-string muscles, the rectus abdominalis, intercostals and sacrospinalis; (2) deep parallel bow-string muscles, the intertransversarii; (3) superficial transverse traction torsion muscles, the trapezius, latissimus dorsi, serratus anterior and pectoralis major, and (4) deep torsion muscles, the semispinalis, multifidus and long and short rotator muscles.

Of these classifications the old one of Meyer[26] seems the best. Judson's[12] paper dealt primarily with the cause of rotation. He showed a model in which he had mounted an articulated spine inside a rectangular wooden frame. His group of transverse muscles and ligaments were represented by rubber bands connecting the tips of the spinous processes with either side of the frame. A flat flexible brass rod was passed through the spinal canal from the top to the bottom of the frame, its width in the sagittal plane. When this was depressed from the top, it must needs bend to the side. His transverse muscles held the spinous processes in the midline, and the bodies rotated toward the convexity. The same objection may be raised to Carey's[28] recent models, that the spinal muscles are not attached to outside, independent supports but to parts of the trunk which move in coordination with the spine. Mackenzie[27] ignored the most important flexors of the spine, those anterior to the trunk, and classified the quadratus lum-

25. Steindler, A.: Diseases and Deformities of the Spine and Thorax, St. Louis, C. V. Mosby Company, 1929.

26. Meyer, H.: Lehrbuch der physiologische Anatomie, Leipzig, W. Engelmann, 1856.

27. Mackenzie, C.: The Action of Muscles, ed. 2, New York, Paul B. Hoeber, Inc., 1930.

28. Carey, E. J.: Scoliosis: Etiology, Pathogenesis and Prevention of Experimental Lateral Curvature of the Spine. J. A. M. A. 98:104 (Jan. 9) 1932.

borum as a flexor. The quadratus is most effective in side bending. But its origin and insertion are both posterior to the nuclei of the lumbar disks, and it can be felt to contract strongly on both sides in pure extension movements. Carey's [28] classification is more anatomic than functional.

I propose classification of the muscles affecting the spine into the following functional groups: .

1. Flexors
   A. Longus colli
   B. Sternocleidomastoid and other anterior muscles of the neck
   C. Rectus abdominalis
   D. Intercostalis externus and obliquus externus
   E. Intercostalis internus and obliquus internus
   F. Psoas major

The longus colli has the distinction of being the only muscle, except the diaphragm and a part of the psoas, attached to the spine anterior to the axes of motion, the nuclei pulposi. The important flexors are those stretched over the anterior surface of the trunk, continuous from the skull to the pelvis, with the interposition of sternum and ribs, and not touching the spine at any intermediate point except through the medium of the ribs. These are properly bow-string muscles. The oblique intercostal and abdominal muscles are important rotators of the entire trunk. Their action rotates the spine with the trunk, but does not produce torsion of the type seen in scoliosis. Combined action of the obliques on one side produces pure side bending with no direct rotary effect on the spine. Although the psoas major is primarily a muscle of the lower extremity, it is usually classified as a flexor of the spine and on the articulated spinal model the direction of its pull caused flexion of the lumbar spine in spite of the fact that the bulk of its attachment lies a little behind the nuclei.

2. Extensors
   A. Interspinales
   B. Sacrospinalis-iliocostalis lumborum, dorsi and cervicis and longissimus dorsi, cervicis and capitis
   C. Intertransversarii
   D. Semispinalis capitis, cervicis and dorsi
   E. Splenius capitis and cervicis
   F. Multifidus

As bow-strings the extensors are only a series of short bow-strings. Considered as a group they are attached to each vertebra consecutively. Because of this important contrast to the flexor muscles they had better not be called bow-strings at all. With the exception of the central fibers of the interspinales, all the extensors are attached laterally, as

well as posteriorly to the axis of motion; acting asymmetrically, they produce side bending. The semispinalis cervices and dorsi, both splenii and the multifidus, connecting spinous processes to transverse processes or to the mastoid, also belong to the next group.

    3. Deep Torsion Muscles
        A. Rotatores
        B. Multifidus
        C. Semispinalis cervicis and dorsi
        D. Splenius capitis and cervicis

All but the rotatores are also extensors. Their general plan of arrangement is from transverse processes to spinous processes of vertebrae at a variable distance above.

    4. Transverse Traction Muscles
        A. Transversus thoracis and abdominalis
        B. Trapezius
        C. Rhomboids
        D. Latissimus dorsi
        E. Sacrospinalis
        F. Quadratus lumborum

This group corresponds to Carey's [28] transverse traction torsion muscles and to Judson's [12] group of those connecting the vertebral column with the shoulders, the thoracic and abdominal parietes and the hips. The muscles connecting the scapula with the shoulder and those connecting the scapula and shoulder with the wall of the chest belong to this group indirectly. Except for the transversi and for the middle portion of the trapezius they are not really transverse but diagonal, and resemble stays supporting a mast.

    B. Mechanics of Muscle Pulls: I shall take the last group first, the transverse traction muscles. Judson [12] showed models, as previously described, in which the spine was passively bent to the side and the passive action of transverse bands between the spinous processes and an outside frame caused rotation of the bodies toward the convexity (fig. 6*A*). Carey's [28] models show a spine which tends to remain straight because strung on a vertical spiral spring and which is actively pulled into a curve by the elasticity of springs passing between spinous processes and an outside frame (fig. 6*B*). This kind of pull causes rotation of the bodies toward the concavity.

    The important fault in both demonstrations is the hypothesis of independent outside supports as origins of muscles. The arrangement of transverse muscles on a chest supported by a spine is represented schematically in figure 7*A*. In this schema the upper trapezius and levator scapulae and the lower trapezius and latissimus dorsi are represented as symmetrical in order to hold the ends of the curve in the
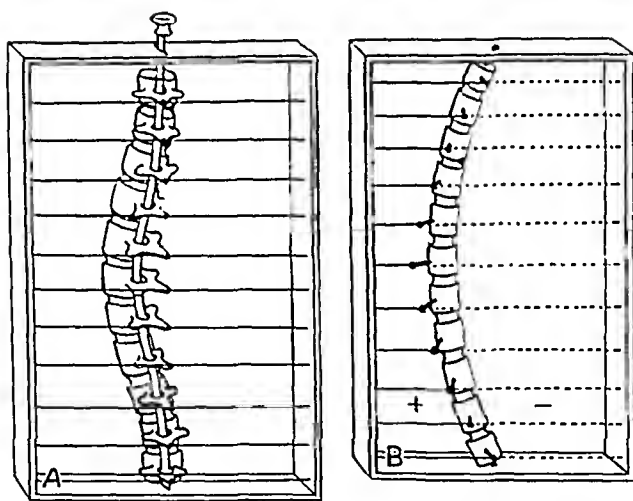
Fig. 6.—*A*, passive transverse pull (Judson). Rotation of bodies toward convexity. *B*, active transverse pull (Carey). Rotation of bodies toward concavity.
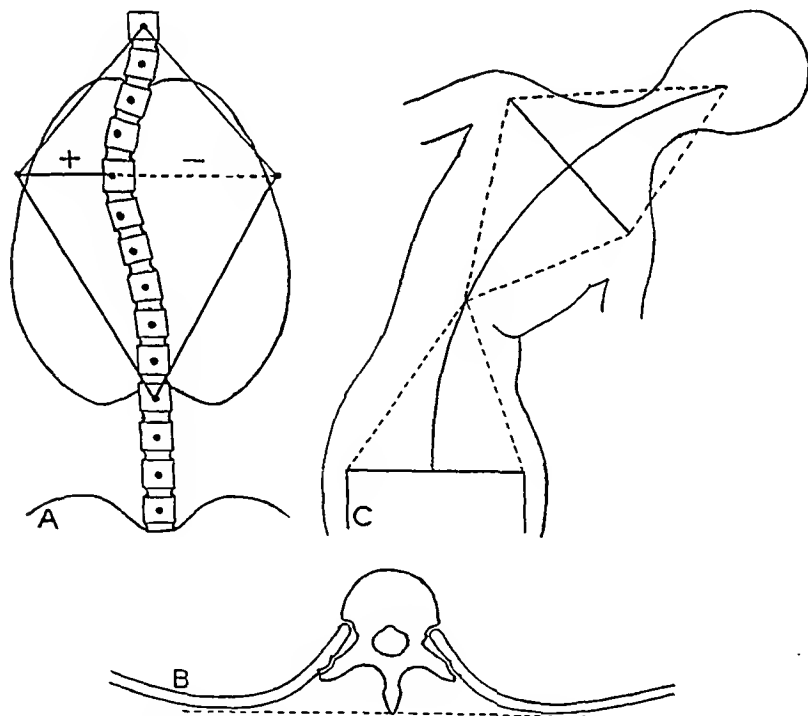
Fig. 7.—*A*, schema illustrating arrangement of transverse muscles on the chest, supported by the spine. *B*, relation of the ribs to the spine and the pull of the transverse muscles. *C*, effect of diagonal muscles.

midline, and the middle portion of the trapezius is stronger on the left than on the right. It is seen that asymmetry of truly transverse muscles produces a curve that is convex on the side of the stronger muscle, with a tendency toward rotation of the bodies toward the concavity. Figure 7B illustrates how well the ribs, from which the transverse muscles eventually take origin, are locked into the spine by the pull of these very muscles, and at what a marked mechanical disadvantage they are in producing rotation.

The effect of diagonal muscles, the stays of the spinal mast, is represented in figure 7C. A spinal curve convex to the left is shown, with pelvis and shoulder girdle indicated in their relative positions. For clarity, the three pairs of dotted lines may represent, from above downward, the upper trapezius, the latissimus dorsi and the quadratus lumborum. It is readily seen that all muscles on the left, the convex side, are elongated. The rotation effect of these muscles is dependent on whether they are active or passive. In an upright spine bent in this fashion all the muscles on the left would be active in resisting gravity, and the effect of their pull on the spinous processes would be rotation of the bodies toward the concavity. If gravity were removed, as in side bending from the horizontal position against gravity, the diagonal muscles on the right, concave, side would be actively contracted and effect rotation of bodies toward the convexity. In actual cases of paralytic scoliosis the deformity may be to either side. Steindler,[25] Moffatt [29] and others have noted the capacity of patients for throwing the weight of the trunk toward the paralyzed side, leaving control of movement to sound muscles on the convex side. The rotation effect of this group is slight; I think it better not to call them rotation muscles.

The group classified as deep torsion muscles undoubtedly rotate the spine. The action of each individual muscle is to rotate the entire trunk above, turning the bodies to the side opposite the active muscles. All of them acting on one side would produce a spiral twist of the spine, each vertebra tending to retain its normal relation to the plane of the trunk at its own level. As indicated by Fergusson,[30] for imbalance of these muscles to produce the deformity typical of scoliosis one must suppose weakness of rotators on one side below the apex, and on the opposite side above the apex, of each curve. It is difficult to imagine such a scattered imbalance occurring primarily with the regularity with which the typical deformity occurs. I believe it better to think of this group, aided by the oblique muscles of the chest and

29. Moffatt, B. W.: The Operative Treatment of Scoliosis, J. Bone & Joint Surg. **10**:316, 1928.

30. Fergusson, A. B., in discussion of Carey.[28]

abdomen, as producing spiral rotation of the entire trunk, and to look elsewhere for the cause of that rotation typical of scoliosis.

The flexors and extensors are all arranged more or less parallel to the spine. There is this important difference, that, whereas the flexors are arranged as a bow-string from one end of the spine to the other without contact with intermediate vertebrae, the extensors are attached to successive vertebrae. The mechanical significance of this in reference to rotation can be demonstrated on the flexible tubing previously described as well as on the articulated spine. Figure 8A shows the 17 inch tube mounted as before, with flexors represented by a rubber band stretched between the heads of pins placed anteriorly near either end and extensors by short bands connecting a series of pins placed posteriorly. Lowering the cross-bar causes a forward or backward curve, depending on the relative tension of the anterior and posterior bands. Using a loose wire loop to produce lateral curvature from either position produces a rotation of the type typical of scoliosis, that of the bodies toward the convexity. Both anterior and posterior bands tend to remain in a straight line. The anterior band meets no resistance, while the posterior band in its attempt draws the posterior processes toward the midline, rotating the bodies toward the convexity. This effect may be expected from all of the extensors as they are all attached posteriorly to the axes of motion. It accompanies side bending in either flexion or extension, though it is more marked in flexion because the extensors are under greater tension.

The same phenomenon is illustrated in a mount of actual vertebrae (fig. 8B). A skeleton of lumbar and dorsal vertebrae is reconstructed by gluing pads cut from a close-meshed rubber bath sponge between the bodies to represent disks. The last lumbar vertebra is mounted on a block of wood with its top surface at 40 degrees to the base. In order to bring this highly flexible column under control, a rubber tube is threaded loosely through the neural canal and attached to a cross-piece above. The spine now tends to assume the normal anteroposterior curves, but is freely movable in all directions within the limits allowed by the articular facets. Flexors are represented by a long rubber band from a nail driven into the anterior surface of the first dorsal to a point in the base corresponding to the symphysis pubis. An elongated toy balloon was interposed between the flexor band and the spine to represent the hollow cavity of the trunk, but was discarded because of the difficulty of keeping it in place during manipulation of the spine. Extensors are represented by short bands joining tacks driven into the tips of the spinous processes. When the spine is pushed into lateral curvature, typical rotation occurs, as with the "flexible rod" model, and for the same reasons.

An even more striking cause of rotation is explained by a study of the mechanics of the extensor muscles. The arrangement is peculiar in that the great mass of muscles lying on either side of the spine produces both extension and side bending, that the extensors are attached
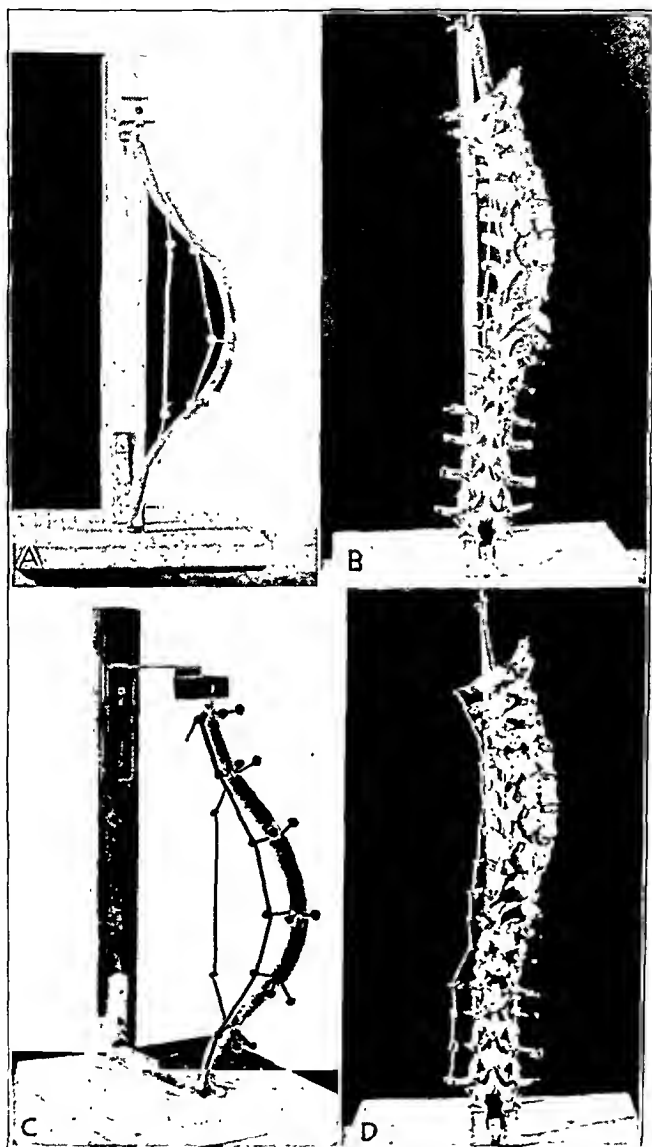
Fig. 8.—*A*, symmetrical flexible rod (rubber tube) mount, illustrating the rotation produced by extensor muscles connected in series as compared with the long bow-string arrangement of flexor muscles, a static effect in lateral curvature from any cause. *B*, same phenomenon produced in a mount of actual vertebrae. *C*, rubber tube mount illustrating the dynamic effect of extensor muscles, relaxation on one side producing lateral curvature, rotation and kyphosis. *D*, same process illustrated in a model of the spine.

lateral to the ball and socket axes of motion and that the side benders are attached posterior to the same axes. The significance of this arrangement may be illustrated on both the symmetrical flexible rod and on the articulated spine. On the rubber tube (fig. 8C) a series of common pins is stuck into the tube in the posterolateral plane on either side to represent transverse processes. The band representing flexor muscles is used as before. A series of short bands connecting transverse processes represents the extensors. On lowering the cross-bar, flexion or extension is again determined by the relative tension of the anterior and posterior bands. The rotation effects are more marked in flexion, and as weakness or, better, lengthening of extensors on one side is being investigated, enough tension is used anteriorly to produce flexion. If both extensor bands are put under equal tension no lateral bending occurs. If the right extensor is put under less tension, or removed entirely, lateral bending occurs convex to the right, with extreme rotation of the characteristic type. In removing lateral support from the right, one also removes posterior support. The unimpaired action of the bands on the left not only bends the spine to the right but presses forward the transverse processes on the left. The unimpaired flexors press the unsupported transverse processes on the right side backward. This produces the typical torsion of bodies toward the convexity of the lateral curve.

The process is equally well demonstrated on the spinal model (fig. 8D). These last demonstrations fall in line with the observation that typical scoliosis is associated with kyphosis. It is possible on the models to regulate the tension of the flexors and asymmetric extensors in such a way that the extensors on the "sound" side balance the flexors, thus producing lateral curvature and rotation without kyphosis. The body is an amazingly correlated machine which tends to compensate any deformity in every way possible. It seems reasonable, therefore, that this compensatory mechanism may account for the absence of a kyphotic element in some scoliotic spines.

INDICATIONS FOR TREATMENT

The fact that unilateral relaxation of extensor muscles produces the three elements of the deformity, kyphosis, lateral curvature and rotation, is evidence in favor of the treatment of scoliosis by extension. It serves to explain the improvement obtained in the lateral and rotary elements by the prolonged hyperextension secured in recumbency on a convex frame.

Figure 8D shows the striking separation of the transverse processes on the convex side which accompanies typical deformity. An operative technic now being worked out has as its object the preven-

tion of all three elements of the deformity by reenforcing the inter-transverse ligaments on the convex side.

SUMMARY

1. The joints of the spine are of rudimentary diarthrodial, double ball and socket type, the axes of all motions being located in nuclei of the disks. The normal anteroposterior curve is not a safeguard against lateral deformity.

2. The deformity in scoliosis consists of lateral curvature and rotation. In many paralytic and idiopathic cases a third element, kyphosis, is typical.

3. Theories of the mechanism of the deformity are reviewed. Typical deformity is not due to changes in articular facets or to pressure from ribs. It is not explained by analogies to a mast with its stays, to a bow with its bow-string or to a column of child's building blocks. It is not explained by the physical laws of flexible rods, either flat or symmetrical. One inherent static property of the spine does favor the typical rotation in side bending, i.e., the expansibility of the column of bodies and the elasticity of the column of laminae and processes.

4. The important muscles affecting the spine are classified into four functional groups and their mechanical effects analyzed.

5. Two mechanical principles by which muscle pull produces typical rotation are described. The first depends on the long bow-string effect of the flexors as contrasted with the attachment of the extensors in series to successive vertebrae. The second depends on the triple action of the erector spinae, relaxation on one side producing lateral curvature, rotation and kyphosis.

6. Hyperextension is the position mechanically favorable for correction of scoliosis. Reenforcement of intertransverse ligaments is suggested as a method of preventing deformity.

ELECTROSURGICAL INCISIONS

HISTOLOGIC EFFECTS

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The purpose of the present work was to study the effects on the tissues of the so-called cutting and coagulating currents, in order to ascertain what specific differences in effects might exist between the two, if any, in the hope of determining the probable damage to the tissues and the rapidity of repair after operations with these currents. The specific effects on several types of tissues were investigated. Sections were made in the skin of the frog, rabbit and dog; various incisions were produced in skeletal and smooth muscle, and the type of tissue lesion was described. Some attempts were made to investigate the histology of blood vessel closure by means of electricity.

The present interest in the employment of the so-called "electric cutting current" devolves on the hope and expectancy of attaining two primary technical advantages:

1. The production of a current which will section vascular tissues and organs difficult of surgical approach, with a concomitant control of capillary hemorrhage.

2. The production of an incision which will approximate a scalpel wound in rapidity and strength of healing reaction without excessive fibrosis.

The first consideration is exemplified in the removal of neoplasms from the brain, and in partial resections of the prostate, liver or spleen, while the second has led to experimentation in intraperitoneal procedures, in which postoperative adhesions are particularly undesirable.

For various reasons, the utilization of electrical machines for surgical purposes, as well as for the treatment of internal diseases, unfortunately attracts a type of practitioner inclined toward extravagant claims. Also, unfortunately, the distinction between cutting operations by electricity and electrocoagulation is not always understood clearly by the operative surgeon who is unfamiliar with the indications for, and the limitations of, cutting and coagulating procedures.

The surgical effects of oscillating currents result from the resistance of the tissues to the current, which manifests itself in the local production of heat and also in the local destruction of the tissues of various and peculiar types.

Interest in the therapeutic possibilities of these reactions began in the late eighties, and followed the discovery by d'Arsonval [1] that muscular contractions (the so-called faradic response) cease when the frequency of oscillation of a current applied to the body is raised above 10,000 per second. A current exceeding this number of oscillations per second, based on d'Arsonval's findings, has been termed a high frequency current, in distinction from a low frequency current. The term "high frequency current" in technical electrical usage is based on other criteria. D'Arsonval, in 1891, suggested the feasibility of passing a high frequency current of 3 amperes through the human body, without producing any sensation in the patient except that of heat. In the same year, Nikola Tesla [2] demonstrated the production of heat within the tissues, by the application of high frequency currents. Doyen,[3] impressed by this demonstration, conceived the idea of producing a localized destruction of tissues by the resistance of the body to high frequency currents, and, after eleven years of experimentation, he presented to the French Surgical Congress, in 1907, a technic for destroying carcinoma with electricity. This method is now termed "electrocoagulation." He considered this method of coagulation by ohmic heat a more satisfactory method than any employed up until that time.

It must be remembered that Madame Curie announced the discovery of radium in 1898, and a decade elapsed before noteworthy contributions were made in its therapeutic application. In 1895, Roentgen discovered the rays known by his name, so that research on the therapeutic effects of radium, roentgen rays and medical high frequency began almost concurrently. During the decade before 1908, Nagelschmidt [4] had been engaged in perfecting a high frequency machine for the coagulation of malignant processes, and in 1908 he presented this apparatus at the surgical congress at Budapest. He described the localized heating effects of high frequency currents as "diathermia."

1. d'Arsonval, A.: Action physiologique des courants alternatifs à grande fréquence. Arch. de physiol. norm. et path. **25**:401, 1893; Traité de physique biologique. Paris, Masson & Cie, 1901.

2. Tesla, N., and Martin, T. C.: Inventions, Researches and Writings of Nikola Tesla, ed. 3, New York, The Electrical Engineer, 1894, p. 394.

3. Doyen, E.: Traitement local des cancers accessibles par l'action de la chaleur au-dessus de 55°. Paris, A. Maloine, 1910; Arch. d'électric. méd. **17**:791, 1909.

4. Nagelschmidt, C. F.: Lehrbuch des Diathermie, Berlin, Julius Springer, 1913; Ueber Diathermie, München. med. Wchnschr. **56**:2575, 1909.

These coagulating machines are not to be confused with those producing cutting currents, which seem to be an American contribution to electrosurgery, the first being demonstrated by Wyeth,[5] of New York, before the surgical section of the New York State Medical Society at Rochester in 1924.

It is my purpose to deal with the distinctions in effect on tissues of the cutting current and the coagulating current, so far as such a distinction can be made, and, in a rudimentary way, with the distinction in the quality of the current which produces the cutting and coagulating effects. The commercial machines produced by various manufacturers for these purposes vary greatly in construction and produce a correspondingly great variety in the qualities of the current elaborated. The ohmic resistance is often too great, or too little, to yield the
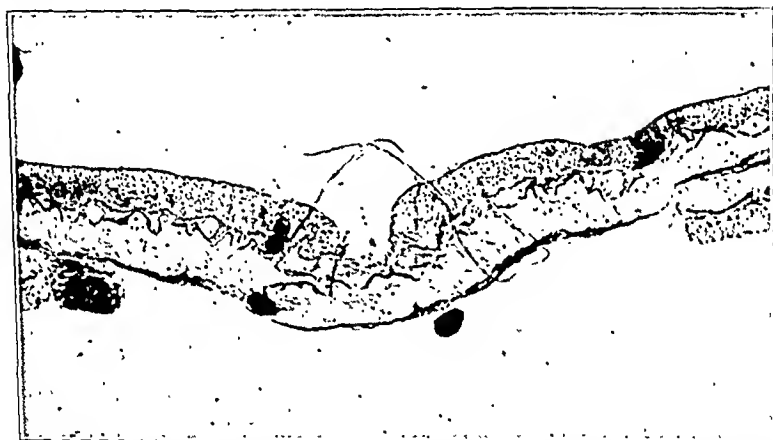
Fig. 1.—Effect of desiccating current on the skin of a frog. The cells near the incision are shrunken without coagulation; × 36.5.

desired effect, and undesired secondary faradic currents, with their resultant neuromuscular response, are induced when improperly constructed machines are employed.

In general, it can be said that raising the amperage produces a coagulating effect, while lowering the amperage and raising the voltage tend to the mechanical disruption of tissue called "electrocutting." The oscillation of current in these surgical machines can be attained in two ways: by means of a set of spark gaps or by radiotrons (radio tubes). The spark-gap machine produces a current from which it is difficult to eliminate damping. This damping is another factor which tends to produce a coagulating current.

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5. Wyeth, G. A.: The Endotherm. Am. J. Electroth. & Radiol. **42**:187 (May) 1924.

THE DAMPED AND UNDAMPED HIGH FREQUENCY OSCILLATIONS

In high frequency current, one deals with oscillations of electrons which perform a pendulum-like movement. As the excursion of a pendulum gets slowly smaller and smaller, on account of friction, gravity and air resistance, in spark-gap machines the oscillations of the electron decrease slowly; they are damped in the gap by the air resistance. We deal, accordingly, in spark-gap machines, with damped high frequency oscillations.

Undamped oscillations may be generated by means of radiotron machines. These machines use the same radiotrons which are used for the wireless and for broadcasting. It is known that in radiotrons a pure current of electrons is flowing, which is rhythmically influenced
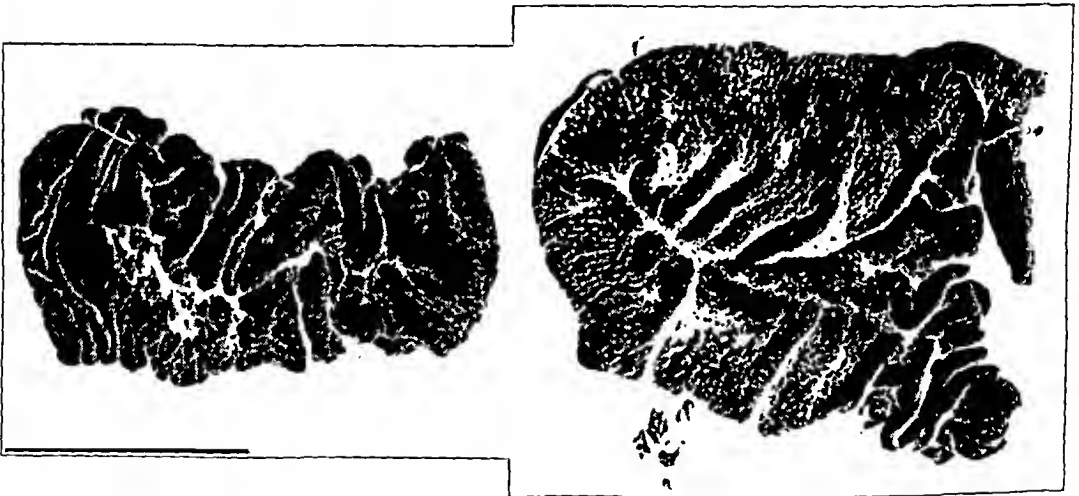
Fig. 2.—The picture on the left represents the average healing of the mucosal surface of the stomach five days after electrical incision; that on the right, a scalpel incision at the same period.

by the continually changing charge of the grid between annode and cathode in the tube. This is the way the oscillations are generated. Since the radiotron is evacuated as far as possible—i. e., free from air— the oscillations are not damped by air or other resistance and are undamped oscillations.

The oscillating currents in radiotron machines have a precisely determined wavelength. In contrast to this, the oscillations of the spark-gap machines are composed of a mixture of waves of different lengths. The present lack of standardization is unavoidable because of the difficulty in measuring accurately the amperage or voltage of a high frequency current during the operation of the machine, so that the proper strength of current used for coagulation, or for cutting, must be learned by experience with each individual machine.

A nice balance must be maintained between voltage and amperage. Also, the capacity inductance and resistance must enter into the determination of the particular current used.

Waller[6] has studied the temperature at which a cutting current operates effectively. An undamped current was investigated. A thermocouple was formed by welding a fine gold wire to a copper needle electrode 0.5 mm. from the tip of the needle, and the ends of the thermocouple were connected to a moving coil galvanometer. Although an alternating potential difference of some thousands of volts is used to form the tiny arc of which the needle is an electrode, while cutting the incision into liver tissue the temperature fluctuation was between 50 and 200 C. This is almost the only attempt to make direct measurements of the physical characteristics of the cutting operation. A wide variation would be expected if various tissues were studied, because of the wide variation of electrical resistance of different tissues.

The production of a cutting current with little or no coagulating effect is now being widely discussed in the German literature by Döderlein,[7] in the Gynecological Clinic of the University of Munich, by Kückens[8] and by Keysser,[9] a former associate of Lexer. The principal French contributors are Champy and Heitz-Boyer.[10]

GENERAL CHARACTERISTICS OF THE CUTTING CURRENT USED ON TISSUES

The technic of electrical cutting is the most recent development in electrical surgery. The electrode glides through the tissues without the necessity of pressure. One has the impression that the tissue melts under the influence of the electrical current. Kirschner,[11] for this reason, has given it the name of "melting cut." This incision has the

6. Waller, M. D.: The Temperature of the Endothermic Knife, Brit. J. Radiol. 4:178 (April) 1931.

7. Döderlein, G.: Das Schneiden mit den elektrischen Funken, Deutsche med. Wchnschr. 52:59 (Jan. 8) 1926.

8. Kückens, H.: Ueber einige bei den Diathermieoperation auftretende Geweberänderungen und über ihre Bedeutung, Beitr. z. path. Anat. u. z. allg. Path. 85:695 (Nov. 20) 1930.

9. Keysser, F.: Die Elektrochirurgie, Leipzig, Gustav Fischer, 1931.

10. Champy, C., and Heitz-Boyer, M.: Mécanisme d'action du bistouri électrique à haute fréquence (effets thermiques et mécaniques des courants de haute fréquence sur les tissus). Compt. rend. Acad. d. sc. 189:1039 (Dec. 2) 1929; Étude des effets mécaniques des courants de haute fréquence: Leur action hémostatique sur les vaisseaux, ibid. 189:1328 (Dec. 30) 1929; Sur l'action hémostatique du bistouri électrique, Compt. rend. Soc. de biol. 103:385 (Feb. 14) 1930.

11. Kirschner, M.: Aus der Praxis des "elektrischen Operierens," Klin. Wchnschr. 9:725 (April 19) 1930.

gross appearance of a scalpel cut. Kelly [12] has called this procedure "acusection," and Keysser [9] has described it as "aukutomy." The histologic effects on tissues can be described in zones, the innermost being a zone of mechanical disruption of tissue and explosion of cells. The mechanics of this disruption has not been determined. The question of whether this effect is produced by molecular dissouation, due to the assumption by the molecules or atoms of the tissues of a new rate of vibration, causing dissolution of the molecular structure, as postulated by Oudin,[13] or is merely a thermal effect due to the sudden expansion of the cell when its liquid contents are converted into steam, which Jellinek [14] thinks the simplest and most logical explanation, is speculative and need not be discussed. Just outside of this zone of tissue disappearance is a zone of elongation or attenuation of cells, this drawing-out effect being seen principally in the nuclei, which are more fluid than the cytoplasm. Kawamura [15] described radiating lines of similarly attenuated cells running out from areas of electrical injury in fatal cases. Depending on the fluidity of the tissues, there is a varying amount of change in the orientation of these elongated cells, so that they tend to come to lie parallel with the direction of the cut. This effect is seen at its maximum in soft connective tissue or muscle, and cannot be produced in the stratum corneum of the skin. In parenchymatous organs, this elongation is transmitted along the nearby blood vessels, perhaps because the tissue surrounding the vessels is less resistant than the vessel wall itself.

Wildermuth,[16] assuming the resistance of a chemically pure physiologic solution of sodium chloride of a temperature of 18 C. as 1, estimated the specific resistance of the various tissues as follows:

Fatty tissue		19.4
Brain tissue	5.5—	6.8
Pulmonary tissue	3.5—	4.0
Liver tissue	2.8—	3.3
Skin	2.5—	3.0
Muscle	1.2—	1.5
Blood (approximate)		1.0

The higher the fluid or blood content of an organ and the lower its fat content, the less is its resistance to electric section. The great

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12. Kelly, H. A., and Ward, G. E.: Radical Breast Operation with Endotherm Knife, Ann. Surg. **42**:88, 1926.

13. Oudin, cited by Lowry, F. P.: The Oudin Current, Am. J. Phys. Therapy **7**:489 (March) 1931.

14. Jellinek, S.: Biologische Wirkungen ultrakurzer Wellen, Wien. klin. Wchnschr. **43**:1594 (Dec. 25) 1930.

15. Kawamura, I.: Elektropathologische Histologie, Virchows Arch. f. path. Anat. **231**:570, 1921.

16. Cited by Keysser.[9]

resistance in cutting through fat, as compared to muscle and skin, at first disturbs the surgeon habituated to the scalpel, which cuts fat more readily than muscle and skin. The variation of resistance to electric cutting necessitates a readjustment of the machine as one passes from skin into fat, and then into muscle or parenchymatous organ.

The Dehydrating Cut.—By a slight change in voltage and amperage, a cutting current can be produced with enough coagulating characteristics to seal the smaller blood vessels along the edge of the cut in an area of so-called "dehydration." This zone is white and presents cells

Fig. 3.—Incision through the wall of the stomach with a cutting current, without a zone of coagulation; × 15.5.

with shrunken contour and pyknotic nuclei, the fluid contents having evaporated. The skeleton contour of the cells is distinguishable. The cytoplasm stains vividly, while the nuclei are hyperchromatic.

GENERAL CHARACTERISTICS OF THE COAGULATING CURRENT USED ON THE TISSUES

This tissue effect is produced *par excellence* by a high amperage and a strongly damped current in a spark-gap machine, or by raising the voltage and amperage of the radiotron machine. A lower frequency of oscillations is necessary than for cutting purposes. Widespread

coagulation can readily be produced with a spark-gap machine without charring or carbonification of the edges of the wound. In the use of this, as in the cutting current, the electrode is brought in contact with the tissues, and then the circuit is closed. If the circuit is closed before the contact is made, sparking across from the electrode to the tissues may result in charring. This zone of charring interferes with the dissemination of the coagulating current and limits the coagulating effect. It is also improper to remove the electrode from the tissues until the current is opened. This sparking from the electrode to the tissues, besides the charring effect, also induces faradic extra currents and muscle jerking which interfere with the delicacy of the operation. Small areas of coagulation assume the form of a half globe or an inverted cone, the base of which is on the surface of the tissue being cut. Two definite zones can be described in the coagulating effect. The inner zone is blanched, and the zone external to this is hyperemic in appearance. The cytoplasm of the inner zone, in histologic preparations, presents a blue nuclear staining, e. g., hematoxylin, contrasting with the red eosin staining of the intact tissue. The tissues so affected are somewhat shrunken, and the nuclei have lost their definition and stain poorly, or disappear. This is the typical picture of coagulation necrosis. The proteins are split, freeing blue-staining acid radicals with a probable increase in the local hydrogen potential. According to Döderlein, the protein hydrosol is changed into a hydrogel. This inner zone passes over into an ill defined outer zone of shriveled cells with pyknotic nuclei and a region of dilated vessels. "The faster the tissue dies, the more it conserves its original form and shape" (Ernest [16]). The primary effect of the heat is identical with necrosis of ordinary skin burns. This applies to preparations made immediately after the operation. Preparations made several hours or days later show the outer zone being invaded by fibroblasts, with round cell accumulation and foreign body giant cell formations. Robertson and Boyd [17] have isolated from the tissues coagulated by heat two immunologically specific toxic proteins. One, diffusible and thermostabile, they term a "neurotoxin," and the other, thermolabile and colloidal, a "necrotoxin." Pfeiffer [18] and Davidson and Mathew [19] have isolated a toxic protein from the urine. It is probable that these toxins produce the outer area of secondary necrosis.

17. Robertson, B., and Boyd, G.: Toxemia of Severe Superficial Burns in Children, Am. J. Dis. Child. **25**:163 (Feb.) 1923.

18. Pfeiffer, H.: Ueber die Ausscheidung eines peptolytischen Fermentes im Harn bei verschiedenen Formen der Eiweisszerfallstoxikosen, München. med. Wchnschr. **61**:1329 (June 16) 1914.

19. Davidson, E. C., and Mathew, C. W.: Plasma Proteins in Cutaneous Burns, Arch. Surg. **15**:265 (Aug.) 1927.

Nieden [20] has pointed out that deep coagulation, even in the inner zone of complete necrosis, is always uneven. In experiments in association with the physicist Weiss, he tried to account for the unevenness and the direction of penetration according to the distribution of stream lines produced by different shapes of electrodes and marked variation of resistance displayed by the various tissues. This variation makes the direction of penetration and deep coagulation unpredictable, and the resulting injury to the tissue perhaps the most dangerous factor one deals with in electrosurgery. After coagulation in the vicinity of large vessels, a fatal postoperative hemorrhage may occur as the result of an unexpected necrosis of the vessel wall.

Fig. 4.—Healing of the wall of the stomach after cutting a current incision without a zone of necrosis; × 16.

SPECIFIC EFFECTS ON DIFFERENT TISSUES

Skin preparations were first studied to determine the type of injury produced by the minimum amount of cutting and coagulating current which would leave a visible impression on the surface. Later, attempts were made to incise the skin of the human being, dog, rabbit and frog with a current producing a purely cutting effect without necrosis. In all skin possessed of a stratum corneum, i. e., in all types employed except that of the frog, a specific cutting effect without coagulation could not be accomplished. A narrow margin of coagulation bounded every incision, although this was narrower (a minimum of 1 mm.) with the cutting than with the coagulating current. The stratum

20. Nieden, A.: Das Anwendungsgebiet der Elektrochirurgie, Zentralbl. f. Chir. **30**:1897 (July 27) 1929.

corneum, then, resists the disruptive effect of the cutting current until enough heat is produced by tissue resistance to cause coagulation. At the time of incision, the epidermis is blanched and is thinner because it is shrunken. The individual epithelial cells can no longer be discerned plainly in the stratum corneum, while in the strata mucosa and germinativa the cells assume somewhat the appearance of those in a normal corneous layer. The cells in the basal layers are shrunken together and have dark, spindly nuclei. The fibers of the connective tissues of the corium are either coagulated adjacent to the cut or have lost their fibrillary structure and appear as conglomerate masses, often resembling hyalin in appearance. They can no longer be dyed red in a hematoxylin-eosin preparation, but stain slightly blue. Between these close-pressed masses appear shrunken nuclei. When the cut reaches into the fat, only the connective tissue of the fat is changed, the fibers being broadened and dyed blue, containing pyknotic nuclei. In the stratum reticulare of the corium, flattened gas bubbles appear. Keysser,[9] and Schridde [21] seem to be the first to describe this phenomenon, and Schridde saw it also in the epidermis. In the skin of the rabbit, connective tissue changes extend around the sweat glands at some distance from the region of the incision, and the hairs are fragmented in the changed area around the cut.

The necrosis produced by the minimum of coagulating and cutting current, which will leave a visible impression on the surface of all the skins provided with a stratum corneum, presents no difference in type of tissue injury from that of coagulation previously described. It is concluded, then, that it is not possible to produce a purely cutting effect without some necrosis on a skin with a horny layer. This slight necrosis, produced by the cutting current, does not, however, always preclude healing by primary intention, as I found in another experiment,[22] performed to test the tensile strength of wound healing on dogs' skins, that 60 per cent of electrically produced wounds showed primary union in comparison with 97.5 per cent of primary union in scalpel wounds. When union did occur, however, the electrically produced wounds were somewhat weaker than those produced by the knife until approximately the twenty-fourth day of healing.

In the midperiod of healing, the electrically produced wounds are notably weaker. At twenty-four days, the two curves have not yet

21. Schridde, H.: Die elektrischen Strommarken der Haut, Centralbl. f. allg. Path. u. path. Anat. **32:**369 (March 15) 1922.

22. Ellis, J. D.: The Rate of Healing of Electrosurgical Wounds as Expressed by Tensile Strength, J. A. M. A. **96:**16 (Jan. 3) 1931; Attempts to Express Mathematically the Healing of Electro-Surgical Wounds, Surg., Gynec. & Obst. **52:**516 (Feb.) 1931.

approximated, when heavy dehydration is employed. That is to say, the attainment of a maximum of strength is delayed in the electrically produced wounds.

The effects of the cutting current on skeletal muscles and the muscular wall of the stomach and intestines were studied. Incisions may be freely made without any zone of coagulation whatever. There are a change of orientation and shape of the superficial cells and a sealing of the capillaries and lymphatic channels. These incisions heal with approximately the same tensile strength as cuts made with a scalpel and without secondary necrosis or infection. Tests on muscle section and healing show no important weakness of the electrically produced wounds at any period of healing. A comparison in healing of electric and scalpel gastrotomy presents curves of healing for the electrically produced wounds, considered as to both rapidity and time of attainment
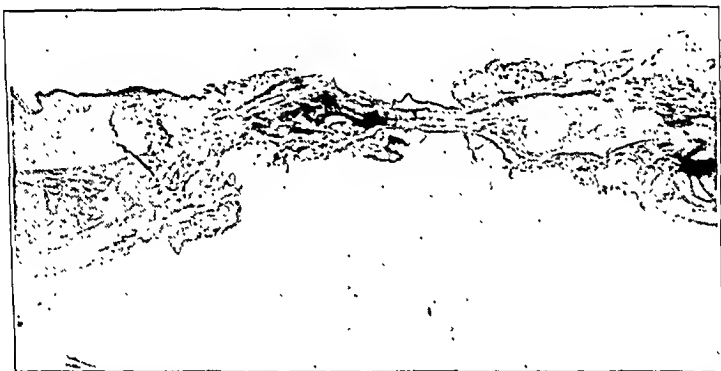
Fig. 5.—Electric ligation of the vein, with some shattering and explosive effect, due to sudden application with too great current density; × 15.5.

of maximum strength, entirely comparable to the scalpel wounds of the muscle wall of the stomach.

The explanation of the failure of the skin with a corneous layer to give the uniform primary healing which muscle displays after section with a cutting current and to present a narrow border of necrosis when enough current density is displayed to section such skin, probably lies in the fact that keratin, the principal constituent of the corneum, has a high electrical resistance. It can, in fact, be employed as an insulator. When enough current density is employed to penetrate this layer, some coagulation of the contiguous, less resistant skin layers invariably results.

Primary mesodermal healing presupposes two factors, that is, a deposition of a complete fibrillary fibrin network across the wound and satisfactory cellular fibroplasia. Hartwell[23] and others have shown that

23. Hartwell, S. W.: Surgical Wounds in Human Beings, Arch. Surg. **19**:835 (Nov.) 1929.

fibrin and collagen are deposited in primary healing by a chemical reaction from "prefibrin" by the absorption of the edema fluid of a wound. This appears to them to be entirely or largely independent of cellular activity and conditioned by the hydrogen potential of the wound. Fibroplasia occurs first by stereotropism of wandering tissue cells or clasmatocytes, along the fibrin network, and, later, by proliferation of these cells. This mechanism was described in 1914 by Harrison,[24] and his work has been studied and corroborated recently by Baitsell,[25] Wereschinski[26] and Carrel.[27] The latter has shown that the formative stimulus to fibroplasia is not found in the blood plasma, but is a local product of the injured tissues. Baker[28] and Hammett,[29] working in Carrel's laboratory, found that the formative stimulus does not depend on liberated amino-acids from the wound or adjacent tissues, but is a protein cleavage product containing a sulphydryl group. The elaboration of this essential stimulus for cell multiplication is apparently not interfered with by the cutting current applied to the muscle or stomach, and, in some instances, to skin. The production of a fibrillary fibrin network is generally not demonstrable after electrosurgery. Following the advice of Hertzler,[30] I attempted to demonstrate this network with a Weigert-Pal stain, and later with the Kilschitzski modification, but found only a granular fibrin deposition, such as one sees in wounds healing by granulation.

The coagulating current, applied to skeletal muscle and stomach, produces the same inverted zone of coagulation as described in the deeper layers of the skin. The appearance of the coagulated muscle, after a few days, resembles hyalin in a necrotic area ultimately surrounded by a connective tissue capsule or absorbed and replaced by fibrosis.

24. Harrison, R. G.: Reactions of Embryonic Cells to Solid Structures, J. Exper. Zool. **17**:521, 1914.

25. Baitsell, A. G.: Origin and Structure of Fibrous Tissue Found in Wound Healing, J. Exper. Med. **23**:739 (June) 1916.

26. Wereschinski, A.: Beiträge zur Morphologie und Histogenese der intraperitonealen Verwachsungen, Leipzig, F. C. W. Vogel, 1925.

27. Carrel, A.: Process of Wound Healing, Proc. Inst. Med., Chicago **8**:62, 1930.

28. Baker, L. E.: Chemical Nature of Substances Required on Cell Multiplication, J. Exper. Med. **48**:163 (Feb.) 1929.

29. Hammett, F. S.: Chemical Stimulus Essential for Growth by Increase in Cell Number, Proc. Am. Philos. Soc. **68**:151 (April) 1929.

30. Hertzler, A. E.: Newer Conception of Wound Healing as Applied to Practical Surgery, Am. J. Surg. **7**:293 (Sept.) 1929; personal communication to the author.

PARTICULAR EFFECTS ON BLOOD VESSELS

The discussion of the effects of these currents on the blood vascular system can be divided, for clinical purposes, into:

1. Capillary hemostasis in vessels of the size which do not usually bleed after the hemostat is removed in ordinary surgical procedure, e. g., laparotomy wounds.

2. The coagulation of moderate-sized vessels, such as the ones which must be ligated before the hemostat is removed.

Fig. 6.—Successful hemostasis with uniform contraction of the wall of the artery without necrosis or pigmentation; × 30.

3. The closure of arteries and veins the size of the radial artery or larger.

Hemostasis in Capillaries, Arterioles and Venules.—When tissues are severed with the cutting current without any zone of coagulation, capillary hemorrhage results, which suddenly ceases a few minutes later, even in such vascular tissue as the muscles or the kidney, with a facility that surprises the surgeon. This unusual effect was first investigated by Heitz-Boyer.[31] He noticed, in histologic preparations, the trans-

31. Heitz-Boyer, M.: Action hémostatique, "secondaire" du bistouri à haute fréquence, Bull. et mém. Soc. nat. de chir. **55**:1946, 1929.

mission of elongation and stretching of the cells of the perivascular
sheath to a point several millimeters from the cut end of the capillary.
There is an abrupt change in the muscular wall of venules and arterioles,
causing contraction and fusion with obliteration of the lumen at the
point of severance. The arteriole, in particular, often becomes tortuous
for a few millimeters. The vascular lumen is occluded by the collapsed
walls and the few epithelial lining cells which are torn off and seen free
in the lumen. In some specimens, no endothelial changes are seen
except a curious, wavelike wrinkling in transverse ridges just at the
point where the lumen begins to contract. It did not appear to Heitz-

Fig. 7.—Correct "electrical ligation" of the artery, showing abrupt diminution
of caliber. The changes are most notable in the muscular layers; the intima is
corrugated but without avulsion of the cells; × 45.

Boyer that the existence of a few avulsed cells in the lumen was suffi-
cient to account for the sudden hemostasis in the capillaries and arterioles
after cutting, and he suspected that there must be a rapid and abundant
liberation of thrombokinase from attrition of the vascular wall. The
following experiment was undertaken. The serum of rabbits' blood
was placed in paraffined tubes. Small, well polished pipets were intro-
duced into rabbits' veins and arteries without touching the edges of
the wounds of entrance. These vessels were then severed from 1 to
2 cm. from the point of the pipet with undamped current and with the
scalpel. The pipets were withdrawn and placed in the tubes containing

rabbits' serum. The pipets from the vessels electrically damaged caused immediate coagulation of the serum, while those from the vessels with the knife wounds caused no coagulation of serum for from ten to twelve minutes, which is the same time that coagulation occurred in the control rabbit serum. He inferred from this that abundant thrombokinase was liberated from the walls of the smaller vessels by the action of the electric current.

Hemostasis in Small Vessels.—Vessels of a size which must be ligated to control hemorrhage in ordinary surgical procedures are not generally successfully obliterated with a cutting current. Either they must be touched with a coagulating current, or the hemostat which

Fig. 8.—Higher magnification to show the typical corrugation without avulsion of the intimal cells at the point of contraction of the vessel; × 65.

occludes them must be touched, in order to produce successful hemostasis. The less tissue surrounding the vessel that is gripped with the hemostat, the less is the area of necrosis formed. The smaller the amount of necrotic tissue, the greater is the chance of absorption of this tissue without a slough, and the chance of infection with secondary hemorrhage from the coagulated vessel. I experimented on coagulation of the splenic vessels and the radicals of the superior mesenteric vessels adjacent to the small intestine in the dog and found that these were best occluded by use of the coagulating current. The walls present the same changes as occur in the capillaries on section. It is possible, however, to exhibit enough coagulating current to break the vessel into fragments and produce hemorrhage, or to explode the brittle, collapsed

and constricted wall a few millimeters from the region of hemostasis. As one becomes more efficient, there is a temptation to employ more voltage for a shorter time. This is dangerous. It is easy to generate a cloud of steam at the point of application, which pushes into the lumen of the vessel and explodes, instead of seals it. It is my opinion that successful coagulation depends on the mechanical effect of constriction of the lumen, and not on thrombus formation. The cells of the muscular layers appear crowded together and stained blue at the point of closure. There are the usual nuclear changes which accompany electric coagulation. The intima is seldom avulsed, and a few free epithelial cells appear in the lumen. If the vessel is coagulated in the solid tissue of an organ, the vessel change does not extend beyond the tissue necrosis in the parenchyma of the organ. This limitation of change was first described by Kuntzen and Vogel.[32] These authors
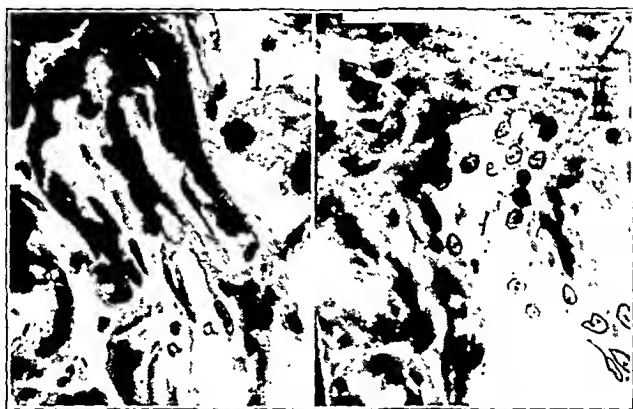
Fig. 9.—*I,* avulsion and elongation of the endothelial cells of a capillary sectioned by a cutting current. *II* represents the more violent action of the coagulating current which sectioned the tissue adjacent to the field shown here. This field is adjacent to the zone of necrosis; × 220.

carried out experiments on rabbits. A lobe of the liver was fixed in the abdominal wall and excised with a coagulating current. The animals were killed on various days. India ink was injected into the portal vein. Thrombi were found to form only as far as the tissue necrosis in the surrounding liver substance. A selective effect of the current on the blood vessels did not manifest itself beyond the region of coagulated liver. No secondary hemorrhages occurred along the vessels. This result agrees with my experience.

Sealing of Vessels up to Six Millimeters in Diameter.—Tinker[33] has described the coagulation of blood in vessels of approximately

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32. Kuntzen, H., and Vogel, W.: Histologische Untersuchungen über die Wirkung chirurgischer Diathermiestroeme, Arch. f. klin. Chir. **164**::39, 1931.

33. Tinker, M. B.: Electro-Surgery with Special Reference to Goiter and Malignancy, Ann. Surg. **94**:587 (Oct.) 1931.

6 mm., extending 12.5 mm. along the lumen. I was unable to demonstrate any such thrombosis in the arteries. In veins a definite coagulation extended not farther back than a distance equal to the diameter of the lumen when the vessel was coagulated with a current strong enough firmly to close but not entirely to destroy the vessel. Even after several days this small, red thrombus was still seen in the vessel merely as a coagulation thrombosis, the definition of many of the red cells being retained, and the white cells appeared unchanged in morphology and distribution. There is no progression in the size of the thrombus, when examined several days after the occlusion of the vessel.

CONCLUSIONS

Two distinct types of tissue effect can be produced by electrosurgical machines. These types of tissue effect depend on the qualities of the current employed. The more the damping and the higher the amperage, the greater is the amount of coagulation accompanying the tissue section. Both the cutting and the coagulating current have special indications and advantages in surgical practice. Massive coagulation of tissues with subsequent sloughing of the necrotic area is undesirable as a surgical procedure. The present electrosurgical technic consists of excising a portion of tissue with the cutting or coagulating current.

Two types of electrosurgical machines are in common use; in one the frequency of oscillation is produced by a multiple spark gap and in the other by radiotrons (radio tubes). The first always produces a somewhat damped current. As the damping is diminished the incision more nearly approximates the scalpel cut. As the damping increases the amount of coagulation increases. The radiotron machine can produce a cut without coagulation, as the current is not damped. By increasing the voltage and amperage in this machine, coagulation results. This is likely to be associated with a charring if the amperage is too high. This prevents penetration of the coagulating effect into the tissues.

Experimental cuts were made with both types of current on the skin of the human being, dog, rabbit and frog. The first three of these have a skin with a stratum corneum, and, in the presence of this layer, some coagulation results before penetration of the skin can be accomplished, even with a pure cutting current. This coagulation does not necessarily interfere with primary healing, but only 60 per cent of the cuts produced in dog's skin healed by primary intention. The skeletal muscle and muscular layers of the stomach and intestine can be severed by a cutting current without coagulation. The phenomenon of vessel closure with a coagulating current is interesting, involving collapse,

shrinkage and agglutination of the vessel walls without extensive thrombus formation. A large amount of thrombokinase seems to be liberated in the cutting of capillaries and small vessels. There are many serious errors to be avoided in the coagulating of vessels. Too rapid coagulation causes explosion and subsequent hemorrhage.

In coagulation of tissues, the specific resistance of the tissues varies tremendously; e. g., fat is more than eight times as resistant as muscle, making the direction of the penetration of deep coagulation uncertain and dangerous.

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INFECTION INVOLVING THE ETHMOID, MAXILLARY AND SPHENOID SINUSES AND THE ORBIT DUE TO ASPERGILLUS FUMIGATUS

REPORT OF A CASE

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Infection of the nose and accessory nasal sinuses by Aspergillus fumigatus is a rare disease. In a careful survey of the literature I was able to find only three cases recorded in which the infection in the sinuses was definitely proved to be due to Aspergillus fumigatus and five cases of aspergillosis of the maxillary sinus of undetermined type.

Aspergillus fumigatus was first described by Fresenius in 1775. This is the commonest Aspergillus and is often found in various cereals, straw, hay and similar substances. It is the species most frequently found in man, giving rise to an aspergillosis of various organs. The spores are very resistant. Aspergilli are generally saprophytes, but they may become parasites. The effects on the human organism are due in addition to mechanical irritation to toxins secreted by the fungi. These toxins have been found to act on the muscular and nervous system of dogs. Harmer and Jockes [1] showed that injection of cultures of Aspergillus fumigatus from the antrum into the ear vein of a rabbit caused the death of the animal in seven days. Postmortem examination showed practically all the organs to be affected, and subcultures yielded pure growth of Aspergillus fumigatus. Bodin and Lenormond,[2] in their researches on the poisonous products of Aspergillus fumigatus, working with guinea-pigs, rabbits and pigeons, showed that there are two distinct toxic substances; one produces tetany and convulsions, the other possesses a depressing or paralyzing power.

There are three varieties of Aspergillus which create most devastation—niger, flavus and fumigatus. More infections arise from the fumigatus than from the niger or flavus types. In man, the Aspergillus fumigatus is most commonly found in the ear (external auditory meatus) and in old abscess cavities in the lung. The mode of infection is not definitely known.

Aspergillus fumigatus is quite familiar as a disease of some birds such as the dove and various other small birds. In them Aspergillus is found in the air passages, and according to some writers produces pneumonia with necrosis of the lung tissue.

In the general population of this country one rarely sees parasites in the nasal passages and their accessory cavities. It is common in India and in people who live in dirt and filth, for example, the Negroes in the South.

In the old literature as far back as 1791 and through the nineteenth century, one finds mention of fungus of the maxillary sinus. The term fungus was used to describe a fungating growth, a spongy mass of morbid granulation tissue or a new growth malignant in character. Hernu[3] and Plaignaud,[4] in 1791, reported cases of fungus of the maxillary sinus. The tissue removed from the antrum was not studied histologically, and cultures were not made. In their cases the history, clinical findings and course of the disease were typical of a malignant growth.

Zarniko,[5] in 1891, reported the first case I could find in the literature of infection of the sinuses due to Aspergillus fumigatus. He stated that, "Aspergillus fumigatus has rarely been found in the nose and never in the sinuses." The patient was white, aged 50, sex not mentioned, and had a chronic suppurative infection of the left maxillary sinus with secondary fungus infection. The chief symptoms were difficulty in breathing through the nose, frontal headache and a thick, greenish, foul-smelling discharge from the nose. Lavage of the antrum showed a mucopurulent discharge and dark brown-grayish material the size of a pea. Microscopic examination showed the presence of a fungus the type of which was believed to be Aspergillus fumigatus, although cultures were not made. The treatment consisted in frequent lavages of the antrum and the internal administration of potassium iodide, from 2 to 4 Gm. a day. The discharge became less, but after sixteen washings the fungus was still found. The patient was not seen again, so the end-result was not mentioned.

Mackenzie,[6] in 1893, reported a case of infection of the maxillary sinus due to Aspergillus mycosis. The patient was a woman, aged 35, who for several years had a chronic, virulent, suppurative infection of

3. Hernu, J. J.: Fongus du sinus maxillaire, abandonné a lui-même; ses ravages; la mort qui les suivit; dissection, J. de chir. **2**:278, 1791.

4. Plaignaud: Observation sur un fongus du sinus maxillaire, J. de chir. **1**:111, 1791; J. de méd. **87**:244, 1791.

5. Zarniko, C.: Aspergillusmykose der Kieferhöhle, Deutsche med. Wchnschr. **17**:1222, 1891.

6. Mackenzie, J. H.: Preliminary Report on Aspergillus Mycosis of the Antrum Maxillaire, Bull. Johns Hopkins Hosp. **4**:9, 1893.

the right antrum in which Aspergilli had developed in large numbers. The chief symptoms were a chronic nasal discharge, swelling of the right side of the face and over the root of the nose and pain over the right eye and in the right ear. A carious second right upper molar tooth was extracted, the antrum was opened, and the floor was perforated with a drill with return of a large amount of pus. The patient refused further surgical procedures, and for two years the antrum was washed out with various antiseptics which failed to cure the condition. She began to pass threads of a false membrane through the opening of the antrum into the mouth. Sections of the false membrane showed numerous Aspergilli which were believed to be of the fumigatus type. Cultures were not taken. The patient was apparently lost sight of as there is no mention of further treatment and of the end-result.

Harmer,[7] in 1913, reported a case of suppuration of the antrum due to Aspergillus fumigatus. The patient was a woman who had suffered many years with hay fever. She had a persistent discharge of mucus from the right side of the nose and occasional thick, membranous, brownish-yellow cast, which looked like wet blotting paper. The odor was not offensive. She had violent attacks of sneezing, occasional headaches and neuralgic pains around the right eye. The right side of the nose was blocked with edematous looking mucous membrane. The right antrum was dull on transillumination. Her general health was bad, her digestion deranged, and she had the appearance of being poisoned. Her nervous system had suffered, and she could not sleep well at night. The temperature and pulse were normal. The antrum was washed out, and cultures on blood agar plates showed a copious growth of Aspergillus fumigatus in forty-eight hours at 37 C. The mycelium were best seen in unstained films, and the fungus grew best on Sabouraud's maltose agar medium. The antrum was washed out twice a day for over a month with various antiseptic solutions without any improvement. She was then given sodium iodide internally, starting with doses of 2 grains (0.13 Gm.) and rapidly increasing the dosage. In forty-eight hours after this treatment was instituted, a great quantity of the membrane came away. At the end of ten days all discharge had ceased, and after three weeks the antrum was clear on transillumination. The symptoms disappeared, the edema of the nose decreased, and the patient's general health rapidly improved.

Tilley,[8] in 1915, reported some details from five cases of aspergillosis of the maxillary sinus. All five of the patients were women. The chief symptoms were: marked nasal obstruction, sneezing, discharge of

7. Harmer, D.: Suppuration of the Antrum Due to Aspergillus Fumigatus, J. Laryng., Rhin. & Otol. **28**:494 (Sept.) 1913.

8. Tilley, H.: Aspergillosis of the Nasal Accessory Sinuses, J. Laryng., Rhin. & Otol. **30**:145, 1915.

mucoid and slightly mucopurulent material, occasional expulsion of small masses of a whitish-gray, semitranslucent, viscous material and neuralgic pains in the cheek and face and pain in the eye. A Caldwell-Luc operation was done in all five cases. The antrum was found to be filled with a semisolid material, the surface of which was smooth and pale grayish blue; this material was extremely viscous and tenacious and loosely attached to the walls of the sinus from which it was separated with little bleeding. The histologic examination of the material removed from the antrum showed a mucinous material simulating an endothelioma with mucinoid degeneration of the stroma. Mycelial threads and hexagonal crystals were present. Cultures were not made, and the type of Aspergillus was not determined. Tilley stated that after operation there was complete relief from symptoms and no recurrence took place.

<center>REPORT OF A CASE</center>

History.—W. B., a Negress, aged 32, a housewife, of Wilmington, Del., came to Johns Hopkins Hospital on Jan. 24, 1931, complaining of prominence of the left eye, swelling of the left side of the nose and nasal discharge. The family history was irrelevant. The past history revealed dengue fever (?) in 1923 with good recovery, adenoidectomy in 1917 and measles in childhood. She had rheumatism in January, 1930, involving most all of her joints, and had been incapacitated for six months. The patient dated the onset of her present illness to six years before admission to the hospital, when she noticed for the first time that the left eye was slightly more prominent than the right. At that time she was troubled with profuse lacrimation of the left eye and headaches. She was examined in the outpatient department of a northern hospital and was told she had a refractive error. Glasses were prescribed, but the symptoms, headache and lacrimation, persisted; dull aching pain in the left orbital and frontal regions and in the left temple was present most of the day every day and was always worse at night. Occasionally the left eye became red, and not infrequently she had a dull pain in the right eye. For six years she had a chronic nasal discharge from the left side of the nose, frequent colds in the head, left-sided nosebleed and difficulty in breathing through the left side of the nose. Three years ago she noticed a slight swelling of the left side of the nose. Two years ago she had diplopia when looking in any direction except straight ahead. This whole picture gradually became worse. The exophthalmos of the left eye became more pronounced. The vision, however, remained good, and her general health had been good. There was no history of loss of weight.

Physical Examination.—The patient was a well developed and nourished Negro woman, 32 years of age, who was not acutely ill. The temperature was 99 F., the pulse rate 80 and the blood pressure 104 systolic and 70 diastolic. Ophthalmologic findings were as follows: right eye, normal; left eye, definite exophthalmos. There was no bruit or pulsation. The lids closed without difficulty. The movement of the left eyeball was slightly limited in the inferior direction. The palpebral conjunctiva of the lower lid and adjacent bulbar conjunctiva were passively congested. The cornea was clear. The pupils were circular and equal, and reacted to light and accommodation. The anterior chamber was of regular depth. The lens and vitreous were clear. The fundi and the fields were normal. Vision in the right eye was 20/20 — 2; in the left eye, 20/70. Examination of the nose

and throat showed the following findings: There appeared to be a thickening of bone below the left orbit and a swelling along the left nasal margin with the maximum point of fulness over the lower portion of the nasal bone, which was definitely tender on pressure. The nasal septum was deflected to the left; the breathing space was very poor on the left side but good on the right. There was a small amount of mucopurulent discharge in the left ethmoidal region; the left inferior turbinate was enlarged. It was impossible to get a satisfactory view of the left ethmoid region due to the marked deflection of the septum. The nasopharynx looked normal. On transillumination, the left frontal sinus and antrum were dark; the right frontal sinus and antrum were clear. There were no enlarged glands at the angles of the jaw or in any of the triangles of the neck. The mouth appeared to be in good condition. The throat and ears were normal. The neurologic examination gave negative results. There was no general glandular enlargement. The heart, lungs, abdomen and extremities were normal.

Laboratory Findings.—The Wassermann reaction of the blood was negative. The hemoglobin (Sahli) was 80 per cent, the red blood cells, 3,290,000, and the

Fig. 1.—Photograph taken before operation, showing swelling along the left lateral margin of the nose, inner angle of the eye and left exophthalmos.

white blood cells, 8,400. The differential count was as follows: polymorphonuclears, 80 per cent; mononuclears and lymphocytes, 20 per cent, and eosinophils, 0 per cent. The urine was normal. The basal metabolic rate was $+11$. Roentgenograms of the sinuses, taken on Jan. 24, 1931 (fig. 2), showed marked clouding of the ethmoids, antrum and sphenoid on the left side, and slight clouding of the left frontal sinus, also some clouding of the ethmoids and antrum on the right side. There was an area which suggested erosion of the orbital plate of the ethmoids on the left side; otherwise the orbit was normal. There was no evidence of Paget's disease. Biopsy of tissue removed from the left ethmoidal region (fig. 5) showed that the gross specimen was grayish, slightly translucent in appearance and firm, but did not have the exact consistency of carcinoma. Its appearance was suggestive of fibrous tissue rather than of tumor. Microscopic examination showed dense fibrous tissue with numerous giant cells. They occurred singly and were not included in definite tubercle formation. One could see in the giant cells bodies having a doubly refractile membrane around them. The doubly refractile bodies were seen in most of the giant cells. Special Gram stain showed myeclial bodies running through the tissue. In places they were branched (fig. 4). A pathologic diagnosis of fungus infection was made. There was no evidence of

tumor in the sections. However, it was suggested that the fungus infection might be a secondary invader and the underlying primary lesion a tumor. A culture was taken from the left ethmoidal region at the time of the biopsy and put on Sabouraud's maltose agar medium. A growth occurred in ten days, which was first greenish in appearance but later turned to a brownish black (fig. 3). Under the microscope one could see mycelial filaments with an enormous number of spores. The mycelial filaments were more or less ramified; frequently they were branched and the condiophorehyphia were much thicker than the mycelial tubes. The conidia were round. Culturally and microscopically, they were typical of Aspergillus fumigatus. Transfer cultures grew out in forty-eight hours and were isolated two or three times.

Diagnosis.—Clinically, the diagnosis was indeed puzzling. The various impressions were mucocele, new growth, tumor involving the orbit, gumma, Paget's disease and osteitis. On the basis of the results of the pathologic and biologic
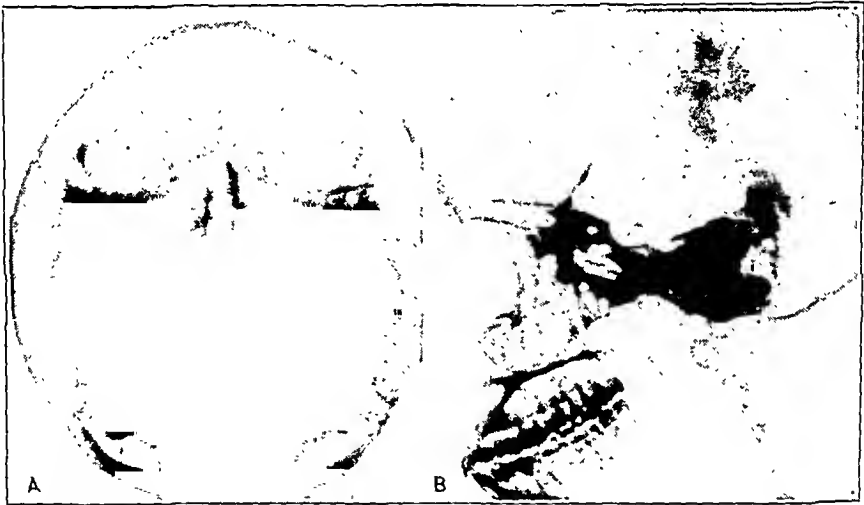
Fig. 2.—Roentgenograms of the sinuses taken on Jan. 24, 1931. *A*, anterior-posterior view, showing clouding of the anterior ethmoids and antrum bilateral, particularly on the left, and slight clouding of the left frontal sinus. There is an area which suggests erosion of the orbital plate of the ethmoids on the left side. *B*, lateral view, showing clouding of the posterior ethmoids and sphenoid on the left.

examinations and the negative Wassermann reaction, a diagnosis was made of infection due to Aspergillus of the fumigatus type involving the ethmoid, maxillary and sphenoid sinuses and the orbit on the left side.

Treatment and Course.—An exploratory puncture of the left antrum beneath the inferior turbinate was made. Neither air nor solution could be blown through the cannula. The trochar felt as if it passed through solid tissue. The nasal septum, which was markedly deflected to the left, had to be straightened in order to get a good view of the ethmoidal region. This was done under local anesthesia on Feb. 10, 1931. The anatomic landmarks on the left were obliterated and the middle turbinate was not seen, but the region of the middle turbinate, ethmoids and middle meatus was filled with tissue which had a grayish-white appearance, was firm and bled easily. There was a moderate amount of purulent discharge in this region. All of the ethmoidal cells were filled with this growth. A biopsy was

made and a culture taken. The pathologic and biologic observations have been previously described. Even after careful cocainization, the ethmoidal region never did seem to become totally insensitive. On account of this and the troublesome bleeding, nothing more was done at this sitting. The incision in the septum was closed with black silk sutures, the left side of the nose was packed with gauze, and the patient was sent back to the ward. The nasal pack was removed the following day.

The patient was then given large quantities of potassium iodide; she received 100 grains (6.5 Gm.) of a saturated solution of potassium iodide by mouth daily, the dose being gradually increased until she was receiving 200 grains (13 Gm.) daily. The following two weeks she complained of almost constant headache, pain in and around the left eye and over the left side of the nose and cheek. The left eye and left side of the nose became more prominent and sore to the touch. The left eye felt weak. The temperature ranged between normal and 101 F.; the

Fig. 3.—Culture from the left ethmoids on Sabouraud's maltose agar medium. A growth occurred in ten days, which was first greenish in appearance but later turned to a brownish black. Transfer cultures grew out in forty-eight hours, and were isolated two or three times.

pulse, between 90 and 120. The potassium iodide began to bring on nausea and vomiting and was discontinued for a few days.

On March 3, 1931, an exploratory operation on the left antrum was done through the canine fossa under avertin-ether anesthesia. The bone in the region of the canine fossa was hard and white, and the outer aspect showed no evidence of necrosis. In using the perforator, hard bone was encountered for a short distance, and then it seemed to enter dense fibrous tissue, which was almost as hard as bone. The left antrum was filled with this tissue. No extensive removal of bone and tissue was attempted at this operation. Bone and tissue were removed for microscopic study, cultures were taken, and a large counter opening was made into the nose beneath the inferior turbinate. A protective gauze pack was placed in the antrum and its end brought out through the nose. The incision beneath the lip was closed with interrupted sutures of 00 plain catgut. The pack in the antrum was removed the following day. It was thought at the time of this operation that

there might be a growth of some kind, the fungus infection merely being a secondary invader. The gross and microscopic appearance of the tissue removed from the left antrum was the same as that removed from the left ethmoidal region, and none of the sections showed anything to suggest a tumor or new growth. The wound beneath the lip soon broke down, and there was a foul smelling discharge. The patient was given smaller doses of a saturated solution of potassium iodide in water, 3 cc. three times a day, which was increased 0.1 cc. per dose a day. This was given by rectum in order to lessen the nausea. Cultures taken from the left antrum three weeks after starting treatment with iodides were negative for fungi. The two bicuspid and first molar teeth in the left upper jaw became loose. The left antrum was kept as clean as possible with irrigations of potassium permanganate. The tissues around the wound in the canine fossa became soft and necrotic, and an opening developed between the left antrum and the mouth. The patient
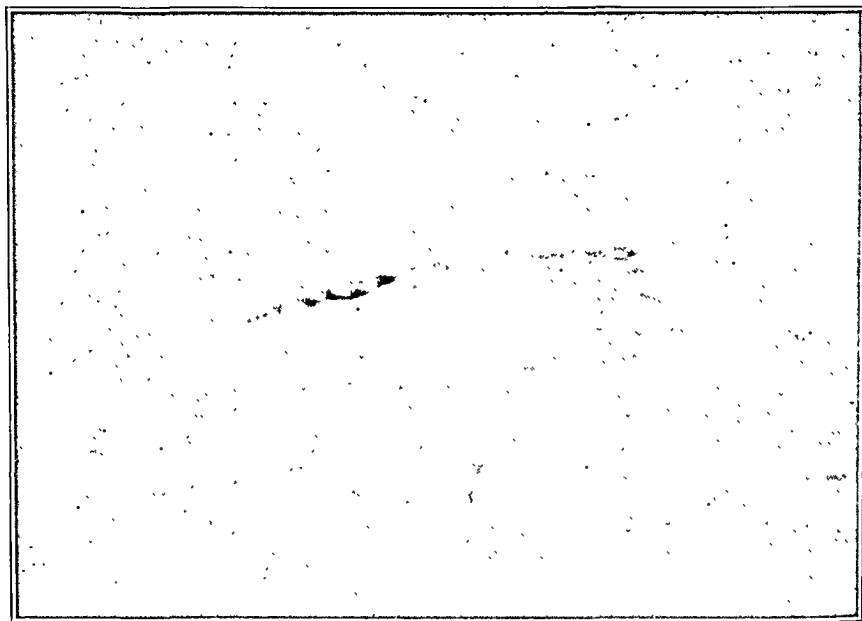
Fig. 4.—Photomicrograph of tissue removed from the left ethmoidal region (high magnification), showing mycelium. The mycelial filaments were more or less ramified, the breadth varying between 2 and 3 microns; frequently they were branched. The condiophorehyphia are much thicker than the mycelial tube, being on the average of about 5 microns in breath. The conidia are roundish. Mycelium were seen best in unstained films. Fungi of the genus Aspergillus, when growing parasitically in the tissues, often lose their characteristics; the typical fructifications are absent, and only mycelial threads and roundish or oval yeastlike bodies are seen. Special Gram stain was used.

continued to complain of headache and pain in the left eye and cheek. The exophthalmos became more pronounced, and the left eye became red with a marked conjunctivitis. The temperature ranged between normal and 102 F.; the pulse between 100 and 120. The patient appeared toxic and was very nervous and irritable, and her digestion was deranged.

On March 18, 1931, under avertin-ether anesthesia, a nasal operation on the ethmoids and sphenoid and a radical operation on the antrum were done on the

left side. As the two bicuspid and first molar teeth were very loose, they were removed. Large masses of dense, hard, fibrous, grayish-white tissue were removed from the left antrum. The surrounding bone, particularly in the floor of the antrum, the nasal wall and parts of the lateral and anterior walls, was soft and came away; it broke off much like wet blotting paper. All of the growth was thoroughly removed from the antrum, and all the surrounding soft bone was removed until hard, normal looking bone was encountered. No defect was seen in the floor of the orbit. The entire lateral wall of the nose was removed, thus making a huge opening into the nasal cavity. The ethmoids were thoroughly cleaned out and found to contain the same sort of growth as in the antrum. The left sphenoid was opened and was found filled with pus and the same sort of growth as in the ethmoids and antrum. The sphenoid was widely opened and as much of the growth as it was possible to take out with safety was removed. The growth extended up around the region of the cribriform plate and as much was removed as possible within the limits of safety. Numerous specimens of the tissue were sent to the laboratory for microscopic study, and cultures were again taken. A protective gauze pack was placed in the antrum and its end brought out through the nose. The opening into the mouth was closed with interrupted sutures of 00 plain catgut. The antral pack was removed the next day.

The following week the temperature ranged between normal and 100 F.; the pulse, between 100 and 120. The wound between the mouth and left antrum soon broke down again with a foul smelling discharge and was kept clean with irrigations of potassium permanganate. The cultures taken from the left antrum, ethmoids, sphenoid and canine fossa were negative for fungi. It is interesting to note that the fungi were not demonstrated in the tissues removed from these regions and the teeth, a special modification of the Gram stain being used, whereas before treatment was started with the iodides the tissue in the ethmoidal region was loaded with fungi which could easily be demonstrated by means of a special stain. The hemoglobin decreased to 62 per cent. The patient was put on a high caloric diet containing 200 Gm. of liver.

Three weeks following the last operation a stomatitis developed—small superficial ulcerations all around the edge of the tongue with sloughing of epithelial tissue. Cultures failed to show the presence of fungi. It was difficult for the patient to take nourishment by mouth on account of extreme pain. Nutrient enemas were given. The stomatitis cleared in a few days with the use of potassium chlorate as a mouth wash. Slight headache continued, the left exophthalmos became a little more pronounced, and the left eye was painful and red, with a conjunctivitis and inflammation of the lacrimal duct, but this improved with the use of irrigations of boric acid. Because of such good vision in the left eye, it did not seem justifiable to sacrifice the eye.

There was a slow but gradual improvement in the patient's local and general condition. The toxemia lessened, and she was not nearly so nervous and irritable. She was discharged on April 29, 1931, after three and a half months' stay in the hospital.

When seen a month later she felt and looked much improved but complained of slight pain over the top of the head. Fluids taken into the mouth would run out of the left nostril. There was a small fistulous opening through the canine fossa between the left antrum and the mouth. The nose and sinuses were clean and free from discharge. The exophthalmos was less marked. There was no pain in the eye or cheek. There was a good breathing space through the nose. The conjunctivitis and inflammation of the lacrimal duct had cleared. Seven weeks later the patient was seen again, and cultures were taken from the nose and sinuses. They

were negative for fungi. When she was seen three months later she had gained 14 pounds (6.4 Kg.) in weight and felt better than she had for several years. She had no headache or pain in the left eye, nose, cheek or jaw. There was no diplopia. Her vision was good. The external swelling of the left side of the nose and exophthalmos were scarcely noticeable. The eyegrounds looked normal. There were no signs of inflammation of the conjunctiva or of the lacrimal duct. The
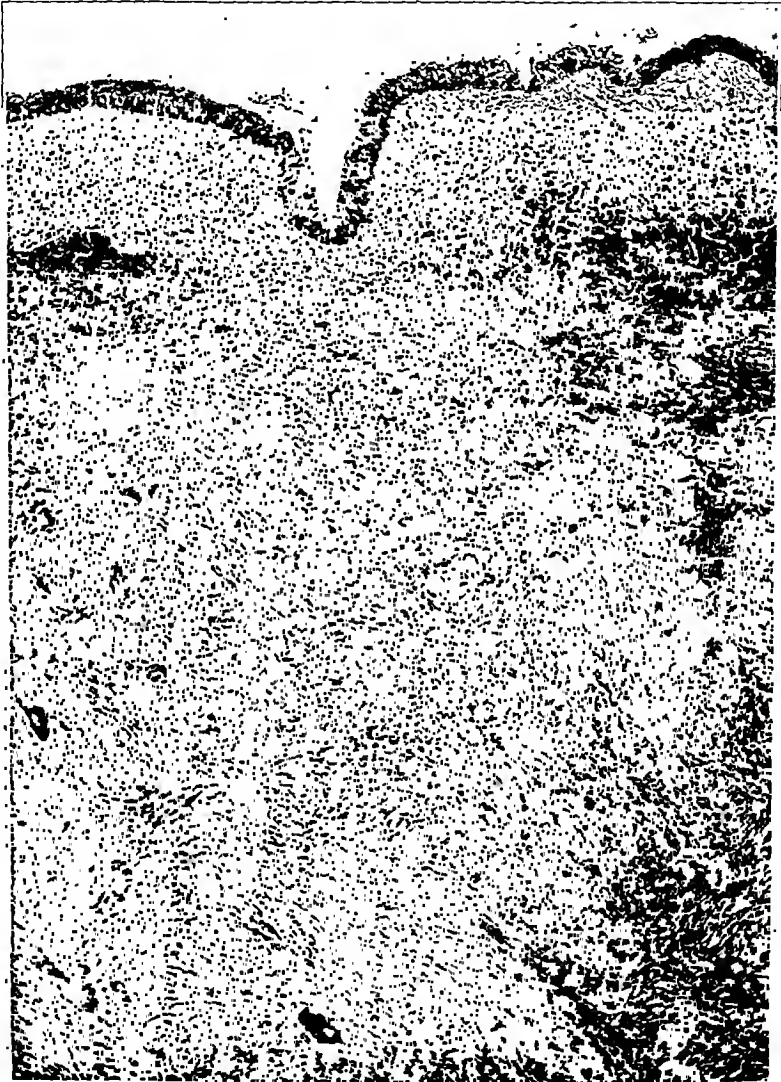
Fig. 5.—Photomicrograph of tissue removed from the left ethmoidal region, showing dense fibrous tissue which in places is almost hyalinized, and numerous giant cells. The giant cells resemble quite strikingly foreign body giant cells. They occur singly and are not included in definite tubercle formation; there is merely a giant cell surrounded by fibrous tissue. Under the microscope one could see oval-like bodies in most of the giant cells which had a doubly refractile membrane around them. Special Gram stain showed numerous mycelia throughout the tissue. In places they were branched. The epithelium is intact and still ciliated in places. The submucosa is edematous and contains mononuclear cells, most of which are plasma cells with some eosinophils.

movement of the left eye was still slightly limited in the outward and downward direction. A small fistulous opening through the canine fossa from the left antrum into the mouth remained. The nose and sinuses were clear and free from discharge. The hard palate looked normal. The patient did not look or feel toxic. She was no longer nervous and irritable, and her digestion was good. The temperature was normal. She was again admitted to the hospital for closure of the fistula opening between the left antrum and the mouth, which was done under avertin-ether anesthesia.

COMMENT

This case is interesting because of the rarity of the condition and because of the extension of the fungous infection, involving not only the maxillary sinus but the ethmoids, sphenoid and orbit. In the cases reported in the literature by Zarniko, Mackenzie, Harmer and Tilley, the maxillary sinus alone was involved. It is also interesting to note that in the eight previously reported cases of fungus infection of the sinuses, seven were in women, in one the sex was not mentioned, and the case reported here was in a woman. The mode of infection is not definitely known. The course of the disease is slow and progressive. In the present case the disease probably existed for six years unrecognized. Clinically, the symptoms are those of a chronic suppurative sinusitis with toxic manifestations. The disease may easily be confounded with an ordinary chronic suppurative sinusitis, mucocele and new growth. Only by careful biologic and pathologic studies can a diagnosis be definitely made. The treatment that was found efficacious in this case was the internal administration of large quantities of a saturated solution of potassium iodide and thorough surgical removal of the growth. After one year the patient was free from symptoms, and there has been no recurrence.

DUODENAL DIVERTICULA

AN ANATOMIC STUDY, WITH NOTES ON THE ETIOLOGIC RÔLE
PLAYED BY DYSTOPIA OF PANCREATIC TISSUE

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Among the historic considerations that we have reviewed on diverticulum of the duodenum, Chomel,[1] in 1710, is credited with having first described the condition. It is believed by most writers, however, that Chomel's case was probably one of dilatation of the ampulla of Vater which contained twenty-two stones. Case,[2] in 1913, first diagnosed diverticula of the duodenum roentgenologically. Forssell and Key,[3] in 1915, diagnosed a case in which the diverticulum was the first to be removed surgically. Linsmayer,[4] in 1919, reviewed the subject from an anatomic standpoint, as did Odgers,[5] Grant,[6] Herbst,[7] Nagel[8] and others, and Spriggs and Marxer,[9] in 1925, gave an excellent summary from a roentgenologic point of view.

1. Chomel, quoted by Buschi: Virchows Arch. f. path. Anat. **206**:121 (Oct. 13) 1911.

2. Case, J. T.: Diverticula of Small Intestine, Other Than Meckel's Diverticula, J. A. M. A. **75**:1463 (Nov. 27) 1920.

3. Forssell, Gösta, and Key, Einar: Divertikel à pars descendens duodeni diagnosticeradt medels röntgenundersökning och operativt aflägsnadt, Nord. med. Ark. **48**:1, 1915; Ein Divertikel der Pars descendens duodeni mittels Röntgenuntersuchung diagnostiziert und operativ entfernt, ibid. **48**:15, 1915.

4. Linsmayer, Heinrich: Ueber Duodenaldivertikel, Verhandl. d. deutsch. path. Gesellsch. **17-18**:445, 1919.

5. Odgers, P. N. B.: Duodenal Diverticulosis, Brit. J. Surg. **17**:592 (April) 1930.

6. Grant, J. C. R.: Duodenal Diverticula, J. Anat. **57**:357 (July) 1923.

7. Herbst, W. P.: Diverticula of the Duodenum, Minnesota Med. **10**:364 (June) 1927.

8. Nagel, G. W.: Unusual Conditions in the Duodenum and Their Significance, Arch. Surg. **11**:529 (Oct.) 1925.

9. Spriggs, E. I., and Marxer, O. A.: Intestinal Diverticula, Quart. J. Med. **19**:1 (Oct.) 1925.

In recent years frequent references have been made to the symptoms and complications which may be caused by duodenal diverticula. This is probably due to the increased significance ascribed to them since they began to be diagnosed by means of the roentgen rays. Scott,[10] in a recent publication, stated that all duodenal diverticula probably eventually cause symptoms, and that they are one of the causes of the chronic condition of the abdomen, together with that of duodenal ileus and splenic drag.

REVIEW OF LITERATURE

Following Chomel, Morgagni,[11] in 1761, described the next case of diverticulum of the duodenum. The nature of the diverticulum is questionable, although Buschi,[12] in his review, mentioned that Morgagni had recorded the first true cause of duodenal diverticulum. Fleischmann,[13] in 1815, reported 3 typical cases. Subsequently, there were occasional reports of cases from postmortem material.[14] Harley's report, in 1857, was the first to appear in English literature. He described a diverticulum containing a large gallstone, and its true nature is questionable. Cruveilhier,[15] in 1849, when writing on diverticula of the gastro-intestinal tract, described pouches in the esophagus and colon, and stated that diverticula did not occur between these two points. Perry and Shaw,[16] in 1893, gave the most detailed report which had appeared since Fleischmann's report; they reviewed 10 cases from the postmortem records of Guy's Hospital from 1826 to 1892, and 4 cases from other sources. Following this, the most noteworthy considerations and reports of cases came from Rolleston and Fenton[17] in 1900,

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10. Scott, S. G.: Diverticula of the Duodenum, Brit. M. J. **1**:346 (Feb. 28) 1931.

11. Morgagni, quoted by Buschi.[12]

12. Buschi, Giuseppe: Beitrag zur Untersuchung der Duodenaldivertikel, Virchows Arch. f. path. Anat. **206**:121 (Oct. 13) 1911.

13. Fleischmann, quoted by Buschi.[12]

14. Habershon, S. O., quoted by Spriggs and Marxer.[9] Harley, George: Specimen of Hepatic-Intestinal Calculus, Tr. Path. Soc. London **8**:235, 1857. Klebs, quoted by Hansemann: Virchows Arch. f. path. Anat. **144**:400 (May 6) 1896. Moore, Norman: Multiple Diverticula of the Small Intestine with Congenital Stricture of the Duodenum, Tr. Path. Soc. London **35**:202, 1884. Roth, M.: Ueber Divertikelbildung am Duodenum, Virchows Arch. f. path. Anat. **56**:197 (Nov. 1) 1872.

15. Cruveilhier, quoted by Spriggs and Marxer.[9]

16. Perry, E. C., and Shaw, L. E.: On Diseases of the Duodenum, Guy's Hosp. Rep. **50**:171, 1893.

17. Rolleston, H. D., and Fenton, W. J.: Two Anomalous Forms of Duodenal Pouches, J. Anat. & Physiol. **35**:110 (Oct.) 1900.

Fischer [18] in 1901, Voigtel [19] in 1904, Bassett [20] in 1907, Gordinier and Sampson [21] in 1906, Keith [22] in 1910, Baldwin [23] in 1911, Buschi in 1911, Bauer [24] in 1912, Davis [25] in 1913 and Wilkie [26] in 1913. Thus far, all cases reported had been found at necropsy. Since the first roentgenologic diagnosis of duodenal diverticulum in 1913, many references to it have been found in the literature, and diverticula are now frequently diagnosed roentgenologically.[27] Numerous instances are reported of removing the diverticulum surgically.[28]

Hypotheses with regard to etiology are as follows: Fleischmann, Keith [29] and Roth stated their belief that herniation of the duodenal mucosa occurred at the points where the duodenal musculature was weakened by penetration of the bile and pancreatic ducts. Letulle and Nattan-Larrier,[30] however, tried to show that the musculature about the duodenal papillae is stronger than that in other regions of the duodenum. Klebs, in 1869, was the first to call attention to the part played by blood vessels in the formation of diverticula of the intestine

18. Fischer, M. H.: False Diverticula of the Intestine, J. Exper. Med. **5**:333 (Jan. 15) 1901.

19. Voigtel, quoted by Spriggs and Marxer.[9]

20. Bassett, V. H.: Duodenal Diverticula, with Especial Reference to Diverticula Associated with the Pancreatic and Biliary Ducts, Tr. Chicago Path. Soc. **7**:83 (Dec.) 1907.

21. Gordinier, H. C., and Sampson, J. A.: Diverticulitis (not Meckel's) Causing Intestinal Obstruction, J. A. M. A. **46**:1585 (May 26) 1906.

22. Keith, Arthur: A Demonstration on Diverticula of the Alimentary Tract of Congenital or of Obscure Origin, Brit. M. J. **1**:376 (Feb. 12) 1910.

23. Baldwin, W. M.: Duodenal Diverticula in Man, Anat. Rec. **5**:121 (March) 1911.

24. Bauer, Theodor: Ueber das Duodenaldivertikel, Wien. klin. Wchnschr. **25**:879 (June 6) 1912.

25. Davis, N. S.: Diverticula of the Duodenum, Tr. Chicago Path. Soc. **9**:1 (Feb.) 1913.

26. Wilkie, D. P. D.: Duodenal Diverticula and Duplicature of the Duodenal Wall, Edinburgh M. J. **11**:219 (Sept.) 1913.

27. Scott.[10] Carman, R. D.: The Roentgenologic Diagnosis of Duodenal Ulcer, Am. J. Roentgenol. **3**:252 (May) 1916. Lockwood, A. L.: Duodenal Diverticula, Tr. A. Res. and ex-Res. Physicans, Mayo Clin. **10**:54, 1929.

28. Forssell.[3] Basch, Seymour: Diverticulum of the Duodenum, with a Report of a Case Diagnosed During Life and Successfully Operated on, Am. J. M. Sc. **153**:833 (June) 1917. Downes, W. A.: A Duodenal Diverticula, Ann. Surg. **76**:43 (July) 1922. Lewis, Dean: A Duodenal Diverticulum, J. A. M. A. **76**:783 (March 19) 1921. Maclean, N. J.: Diverticulum of the Duodenum, Surg., Gynec. & Obst. **37**:6 (July) 1923. Siegrist, Hans: Ein Beitrag zur Kasuistik der Duodenaldivertikel, Cor.-Bl. f. schweiz. Aerzte **49**:47 (Jan. 4) 1919.

29. Keith, Arthur: The Nature and Anatomy of Enteroptosis (Glénard's Disease), Lancet **1**:631 (March 7) 1903.

30. Letulle, Maurice, and Nattan-Larrier: Région vatérienne du duodénum et ampoule de Vater. Bull. et mém. Soc. anat. de Paris **12**:491 (June) 1898.

other than duodenal, and this idea has been reemphasized by Hansemann,[31] Graser [32] and Fischer. Keith also advocated the idea that traction exerted at the side of the common bile duct by ptosis of abdominal viscera and increased intra-intestinal pressure might, in certain cases, give rise to these diverticula. Roth, who was probably the first to advocate the idea of traction, believed that the pull on the duodenum might be exerted by a pancreas which was receding, owing to atrophy. Chomel and Harley concluded that traction might be exerted by scar tissue, and more recently, Davis stated that the superior and inferior pancreatic-duodenal arteries may cause the necessary amount of traction in cachectic subjects. Opposed to the traction hypothesis were Buschi and Jach,[33] who argued that if pull were exerted it would not be confined to isolated small areas of the duodenum, as would necessarily be the case in the formation of duodenal diverticula. They also argued that if an atrophic, receding pancreas were to exert the necessary traction, dense fibrous tissue would have to be interposed between it and the duodenal wall, and this is never found.

Various writers have favored the congenital origin of these structures, among them Buschi, Gandy,[34] Letulle,[35] Marie [36] and Wilkie. Buschi argued that the duodenum shows a predisposition to congenital anomalies because it is the portion of the intestinal tract which undergoes the greatest changes during fetal development. He quoted Shaw, who found a diverticulum associated with duodenal stenosis in an infant. He also quoted Lewis and Thyng's [37] demonstration of epithelial outgrowths from the duodenum in early human, pig and rabbit embryos, and the association of diverticula with accessory pancreatic tissue. Other arguments in favor of the congenital origin are the facts that duodenal diverticula may be accompanied by other gastro-intestinal diverticula,[26] and that they are seldom associated with inflammation or dilatation of the duodenum itself.[9]

31. Hansemann, David: Ueber die Entstehung falscher Darmdivertikel, Virchows Arch. f. path. Anat. **144**:400 (May 6) 1896.

32. Graser, Ernst: Ueber multiple falsche Darmdivertikel in der Flexura sigmoidea, München. med. Wchnschr. **46**:721 (May 30) 1899.

33. Jach, quoted by Buschi.[12]

34. Gandy, M. C.: Diverticule duodénal congénital, Bull. et mém. Soc. anat. de Paris **2**:691 (July) 1900.

35. Letulle, Maurice: Malformations duodénales. Diverticules périvatériens, Bull. et mém. Soc. anat. de Paris **12**:807 (Dec.) 1898.

36. Marie, M. R.: Diverticules duodénaux périvatériens, Bull. et mém. Soc. anat. de Paris **1**:982, 1899.

37. Lewis, F. T., and Thyng, F. W.: The Regular Occurrence of Intestinal Diverticula in Embryos of the Pig, Rabbit, and Man, Am. J. Anat. **7**:505 (Feb. 29) 1908.

Increasing consideration has been accorded the idea that a congenital muscular defect forms a *locus minoris resistentiae* which is the basis for the later development of intestinal diverticula. [38] The localized weakness is said to be due either to penetration of the bile and pancreatic ducts, or of blood vessels as previously stated, or simply to pathologic changes in the musculature. Andrews,[39] Bassett, Opie,[40] Ribbert,[41] and others made brief statements as to the influence of accessory pancreatic tissue in weakening the wall of the bowel, whereas Hansemann reasserted that traction on the accessory pancreas, as described by Neumann and Nauwerck,[42] was a factor in the production of diverticula of the small bowel. Cases of intestinal diverticula other than duodenal, associated with an accessory pancreas, have been reported by Hanau,[43] Klob,[44] Weichselbaum,[45] Zenker [46] and others, and Gardiner [47] reported a case of a congenital hour-glass stomach combined with an accessory pancreas. Linsmayer, in 1919, to whose paper we wish to draw particular attention, emphasized the influence of the pancreas above all other factors. In addition to the fact that he always found the diverticula in close association with the pancreas, as have other observers, he stated that in the smallest diverticula, which were not fully formed, he found small lobules of pancreas between the muscle bundles; in 3 duodenums without diverticula he found pancreatic tissue embedded in the muscularis externa. He stated that the development of a duodenal diverticulum is dependent on the displacement of pancreatic tissue in the wall of the intestine, which tissue produces a circumscribed *locus minoris resistentiae,* and that duodenal diverticula "are congenital only so far as the predisposition to them occurs, due to dystopia of pancreatic tissue arising in earliest fetal life." In this connection it may be noted that Zenker, in 1861, found an accessory pancreas in 5 cases, lying within the wall of the intestine; 1 of these lay near the tip of a finger-like true diverticulum, 5 cm. long.

38. Nagel.[8] Mayo, W. J.; Wilson, L. B., and Giffin, H. Z.: Acquired Diverticulitis of the Large Intestine, Surg., Gynec. & Obst. **5**:8 (July) 1907.

39. Andrews, E. W.: Duodenal Diverticula, J. A. M. A. **77**:1309 (Oct. 22) 1921.

40. Opie, E. L.: Diseases of the Pancreas, ed. 2, Philadelphia, J. B. Lippincott Company, 1910.

41. Ribbert, Hugo: Lehrbuch der allgemeinen Pathologie und der pathologischen Anatomie, ed. 7, Leipzig, F. C. W. Vogel, 1920, p. 489.

42. Nauwerck, C.: Ein Nebenpankreas, Beitr. z. path. Anat. u. z. allg. Path. **12**:29, 1893.

43. Hanau, quoted by Lewis,[48] p. 441.

44. Klob, quoted by Opie.[40]

45. Weichselbaum, A., quoted by Lewis.[48]

46. Zenker, F. A.: Nebenpancreas in der Darmwand, Virchows Arch. f. path. Anat. **21**:369, 1861.

47. Gardiner, J. P.: A Case of Congenital Hour-Glass Stomach with Accessory Pancreas, J. A. M. A. **49**:1598 (Nov. 9) 1907.

In an attempt to obtain some definite information on the fetal development of the pancreas and duodenum, a brief review of studies on the embryology of these organs was made. Lewis [48] stated that a pancreas both dorsal and ventral has been found in 3 and 4 mm. embryos, and that an accessory pancreas is most frequently connected with the stomach, but also occurs in the duodenum, jejunum and ileum, and "has been frequently found at the apex of a true diverticulum." Lewis and Thyng found epithelial nobs in human, as well as in pig and rabbit embryos, which were interpreted as epithelial diverticula. Helly [49] described the epithelial outgrowth from the duodenum, penetrating the mesoblastic portion of the wall of the intestine.

The development of the well differentiated muscle layers occurs at a much later date than that of the epithelial elements, according to Lewis,[48] who stated that the longitudinal muscle of the duodenum becomes distinct at the 75 mm. stage. He gave no time for the development of the circular muscle, which is probably developed somewhat earlier than the longitudinal; one of us (Dr. Horton [50]) observed that the circular muscle layer in the stomach and duodenum is well developed in a 41 mm. human embryo.

With regard to the form and position of the pancreas in some of the lower vertebrates, Oppel [51] quoted Maas [52] as having found a pancreas-like organ embedded in the serosa of the wall of the intestine in myxine glutinosa, one of the cyclostomas, and Brachet [53] found a ring-shaped mass of cells around the circumference of the midgut beneath the epithelium, in ammocetes. In Salamandra maculata, the longitudinal muscle partially surrounds the pancreas for a short distance.

The clinical significance of duodenal diverticula is still debatable. Baldwin, Bauer, Davis, Fischer and Wilkie reported isolated cases of duodenal diverticula which were believed to have caused obstruction and even death. Occasional cases of perforation have also been reported.[54]

48. Lewis, F. T.: The Development of the Small Intestine, the Large Intestine, the Liver, and the Pancreas, in Keibel, Franz, and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 381.

49. Helly, Konrad: Zur Pankreasentwickelung der Säugetiere, Arch. f. mikr. Anat. **57**:271, 1901.

50. Horton, B. T.: Pyloric Musculature, with Special Reference to Pyloric Block, Am. J. Anat. **41**:197 (May) 1928.

51. Oppel, Albert: Lehrbuch der vergleichenden mikroskopischen Anatomie der Wirbeltiere, Jena, Gustav Fischer, 1900, vols. 2 and 3.

52. Maas, Otto, quoted by Oppel,[51] vol. 3, p. 825.

53. Brachet, A., quoted by Oppel,[51] vol. 3, p. 829.

54. Lucinian, J. H.: Diverticulum of the Duodenum Perforated into the Pancreas, Am. J. Roentgenol. **24**:684 (Dec.) 1930.

Cole and Roberts,[55] in 1920, suggested that possibly primary carcinoma of the duodenum arises from the pancreatic tissue which is so commonly found in the walls of duodenal diverticula. Confirmation of this statement has not been found in the literature. The association of diverticula with duodenal ulcer and cholecystitis has been emphasized by some writers.[56] However, Robertson and Hargis [57] did not mention duodenal diverticula in their report, in which they emphasized shortening of the distance between the ampulla and pylorus in cases of duodenal ulcer.

<div style="text-align:center">MATERIALS AND RESULTS</div>

The material for this study was taken from the postmortem records and specimens of the Mayo Clinic, up to June 1, 1931. The records were first reviewed, and the description was noted of all structures diagnosed as duodenal diverticula. These specimens were then studied, and the final analysis excluded those so-called diverticula which had formed as results of duodenal ulcerations. Pouchings and deep beds of scar tissue in the first portion of the duodenum were frequently designated as duodenal diverticula in the older records, and occasionally even as late as 1923. However, in recent years the pouchings in the region of the pylorus were designated as such, and the deep ulcer-beds were recorded as ulcers. The final material analyzed consisted, therefore, only of those duodenal diverticula which, in the literature, are commonly designated as "false" or "primary" diverticula or as "mucosal hernias," and which we will refer to as "duodenal diverticula."

The total number of duodenums in which diverticula were found was 122, the first one having been recorded in 1913. The total number of diverticula of the duodenum in these 122 cases was 145. One hundred and eight of these occurred singly, whereas in 14 of the duodenums examined 2 or more diverticula were found. In other words, 88.53 per cent of the duodenal diverticula in this series occurred singly, whereas 11.47 per cent occurred as multiple diverticula. Of these multiple diverticula 2 occurred in 8 cases, 3 diverticula in 4 cases, and 4 and 5 diverticula in 1 case each; thus greater multiplicity occurs only rarely. Among those listed as single diverticula are included 7 which were bilocular; that is, they had a single opening but with a subdivision of the sac into two parts by a septum.

A large percentage of the diverticula occurred in close relationship to the major and minor duodenal papillae. The position of the diverticula

55. Cole, L. G., and Roberts, Dudley: Diverticula of Duodenum: Their Clinical and Roentgenological Recognition, Surg., Gynec. & Obst. **31:**376 (Oct.) 1920.

56. Perry and Shaw.[16] Wilkie.[26]

57. Robertson, H. E., and Hargis, E. H.: Duodenal Ulcer: An Anatomic Study, M. Clin. North America **8:**1065 (Jan.) 1925.

with relation to the papilla of Vater was determined either from the protocol or by examination of the specimen in 141 instances. The position in 4 of the 145 cases was not ascertainable. In 82 cases (58.15 per cent of 141), the diverticulum was closely associated with the papilla of Vater (figs. 1, 2 and 3). Thirty-six (25.53 per cent) of the diverticula occurred proximal to the papilla of Vater, and most of these were apparently adjacent to the minor papilla, which frequently contains pancreatic tissue besides the duct of Santorini. Thus, 83.68 per cent of the diverticula occurred in association with pancreatic ducts. Twenty-three (16.31 per cent) of the diverticula were situated distal to the papilla. None was found in the first portion of the duodenum. These statements apply to the position with relation to the long axis of the duodenum. An additional and very important point to be emphasized is the position with relation to the circumference of the duodenum. In every instance, the orifice of the diverticulum occurred on the concave or pancreatic border of the duodenum, and the sac either penetrated or lay against the pancreas. The smaller sacs were buried in the pancreas. Those that were larger were in contact with the pancreas only at the neck of the sac, with the fundus covered by a small amount of areolar tissue, and lying either dorsal or ventral to the duodenum and the pancreatic head (fig. 1 *A*).

The size of the diverticula varied considerably. The diameter of the orifice, which is usually circular, and the depth of the sac were the two measurements most frequently recorded. The smallest diverticulum consisted of a tiny, blind tract which had burrowed down along the intramural portion of the common bile duct for 0.3 cm., its orifice being only 0.2 cm. in diameter and situated at the base of the papilla. The largest diverticulum measured 5.0 cm. in diameter at the orifice, and the sac was 7.0 cm. in depth and lay superior and slightly dorsal to the head of the pancreas. These two cases represent the extremes in size. The average diameter of the orifices was 1.15 cm., the diameters most frequently measuring between 1.0 and 2.0 cm. The average depth of all the sacs measured was 2.01 cm. The depth of the sac varied more than did the diameter of the orifice, but the majority were between 1 and 2.5 cm.

Most of the sacs had orifices which were smaller in diameter than the widest diameter of the deeper portions of the sac; that is, they were flask-shaped (fig. 1 *A*). In a few instances the mucosa at the rim of the orifice was thickened and formed an overhanging thick ridge. In those diverticula which were very small or which, though broad, were still in an early stage, this flasklike characteristic was lacking; the orifice was as large as, or larger, than the widest portion of the depressed area (figs. 1 *B*, 2 and 3).

Microscopically, the duodenal diverticula were found to be primarily mucosal structures, the majority having no muscle layers in their walls.

In those which we believe to be early diverticula, the muscle layers of the duodenum extended for a variable distance down into the wall of the pouch, but were practically discontinued near the fundus of the pouch (figs. 2, 3 and 4). The fundus was thus composed only of mucosa, submucosa and a small amount of connective tissue resting directly on the pancreas, with occasional small, smooth muscle bundles present in the connective tissue at the fundus. In those early diverticula which were situated immediately adjacent to the papilla of Vater or to the
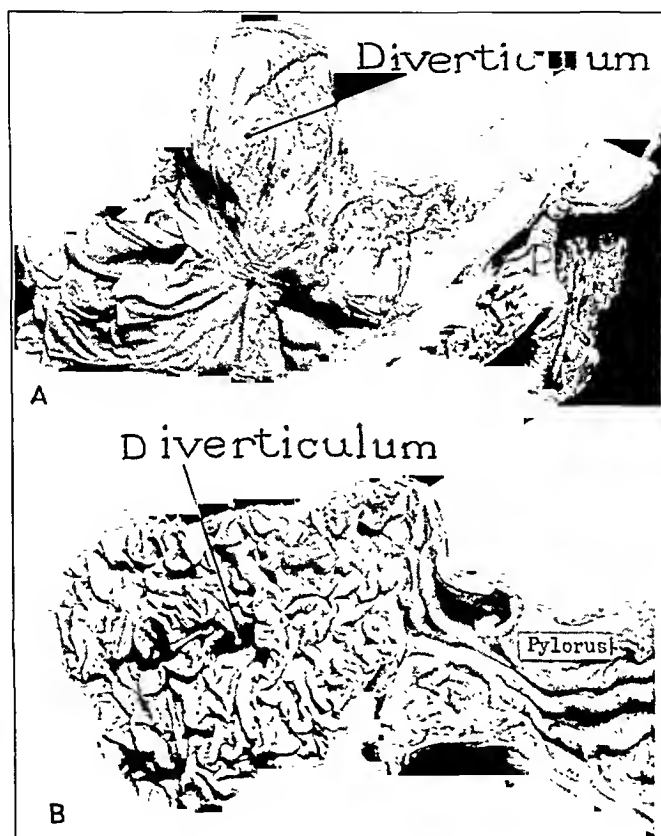
Fig. 1.—*A*, external aspect of large diverticulum from a man, aged 77. The sac is 5 cm. deep. *P* indicates pylorus. *B*, early diverticulum from a man, aged 61. The probe is in the common bile duct, and projects through the ampulla of Vater. A broad, shallow diverticulum and one of a small, shallow type may be observed in this and in figures 2 and 3.

minor papilla, the duct musculature was present on one side of the pouch (figs. 2 and 3). In all of the large and older diverticula, the muscle layers of the duodenal wall stopped quite abruptly at the orifice, leaving the wall devoid of muscle or practically so. Occasionally a few small muscle bundles were found deep at the fundus of the sac, but these were never prominent and had to be searched for carefully. In

two fairly early diverticula, which we believe were destined to be bilocular had the patients lived longer, there were fairly large masses of muscle between the mucosa and the pancreas at the fundus of the pouch. These masses caused low projections upward into the sacs, forming the beginnings of double sacs. The muscularis mucosa was intact in all instances and occasionally seemed to be hypertrophied.

The mucosa in the earlier diverticula was thicker and contained more glands and villi than in the older sacs (figs. 2, 3 and 4). Brunner's
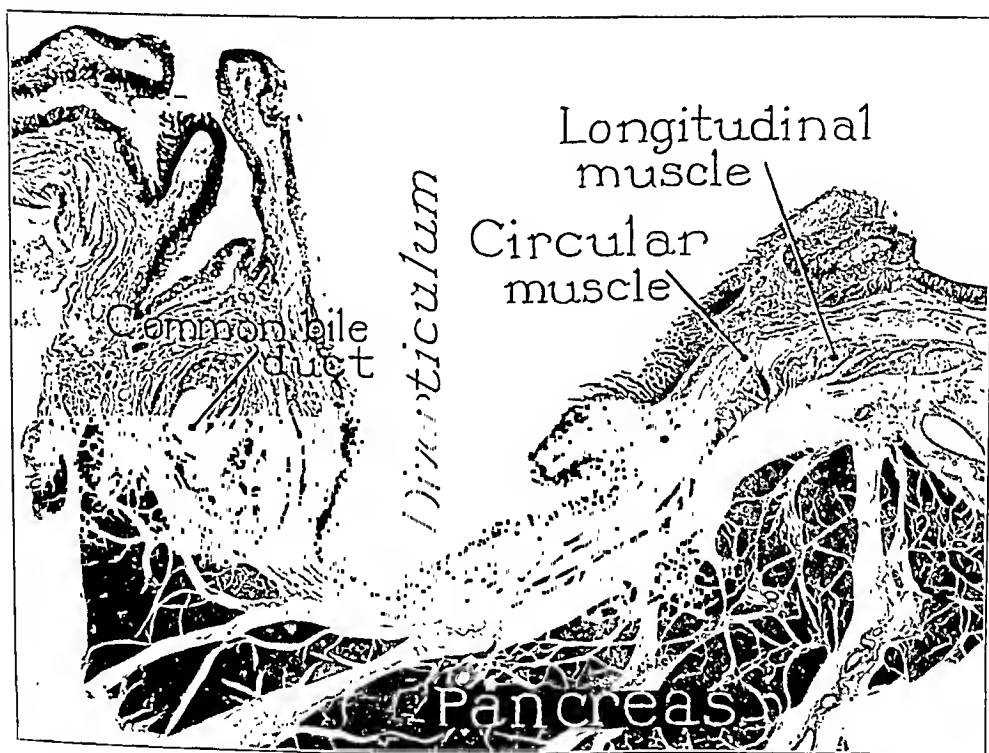
Fig. 2.—Section through diverticulum shown in figure 1 *B*. Strands of muscle tissue almost completely surround the fundus of the sac. van Gieson stain; × 5.

glands in varying proportion were found in a good many of the sections studied, and would, no doubt, have been found more frequently had a greater number of sections been cut from each diverticulum. Lymph follicles were occasionally found. However, in the large sacs of older patients, the mucosa was thin and atrophic, and devoid of Brunner's glands and lymph follicles.

Evidences of previous inflammation were not observed, either in the early or in the old sacs, and no dense connective tissue bundles could be made out beneath the mucosa, as were found in some of the diverticula
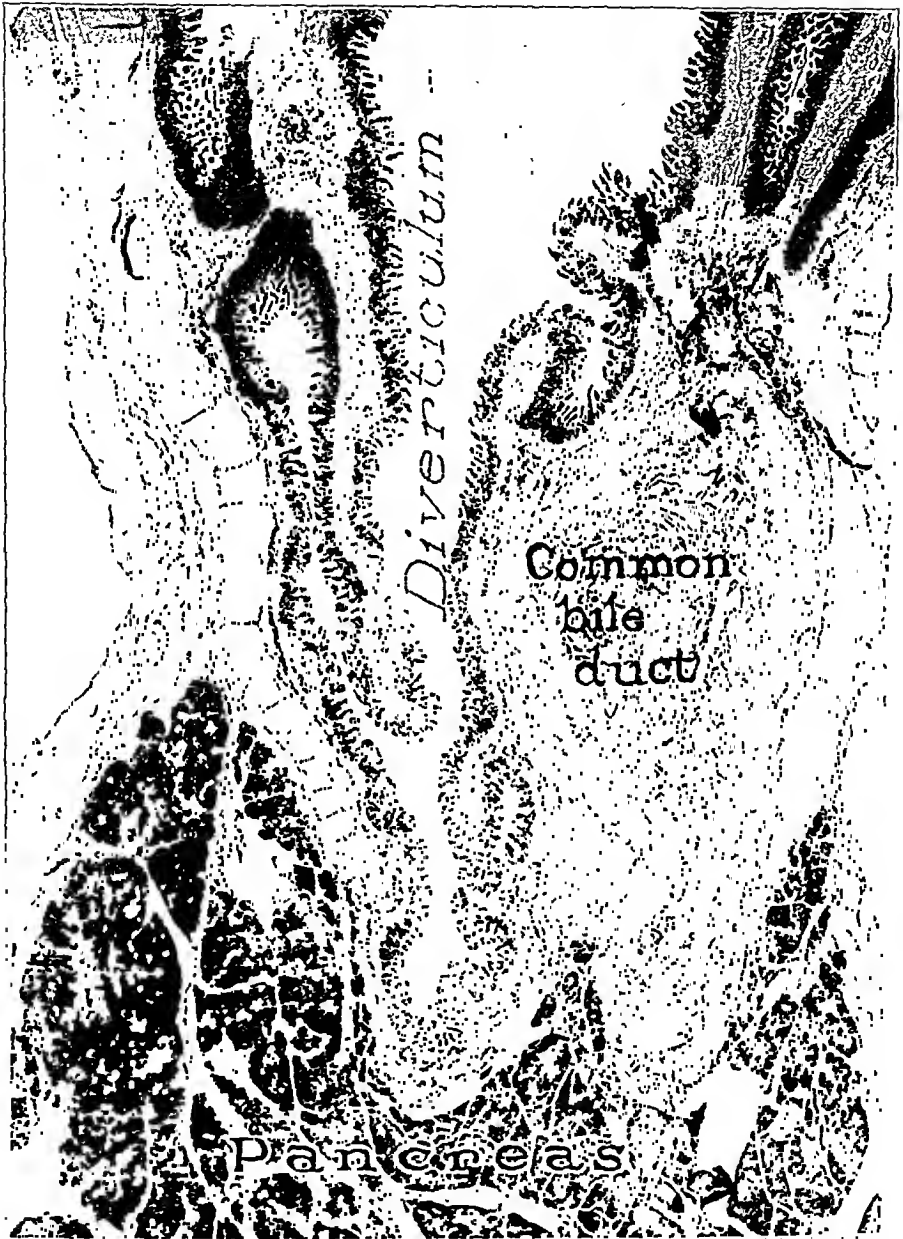
Fig. 3.—Section through a diverticulum which is burrowing down beside the common bile duct. The muscle layers may be seen to end rather abruptly shortly before the fundus of the sac is reached. This is an early diverticulum from a man, aged 61. van Gieson stain; ×8.

of the sigmoid and rectum studied for comparison, although in diverticula of the large bowel also atrophic mucosa and the usual muscle layers were absent.

The age incidence in this series of cases in general corroborates that given in the literature. The average age of the patients was 60.8 years. Most of the diverticula were found among persons who had reached the fifth decade of life, but 15 of the patients were between 40 and 49 years of age, and a few cases occurred before the patients were 40 years. The following gives the distribution by decades for the 122 cases: from less
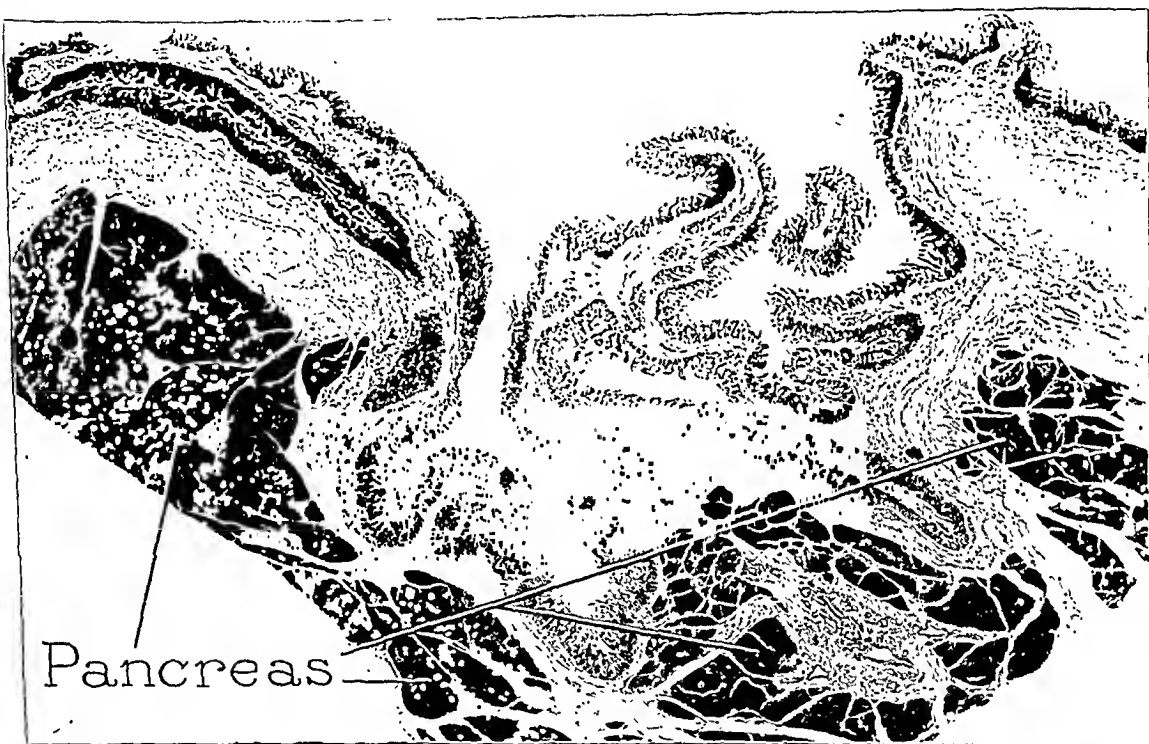
Fig. 4.—Section through an early diverticulum which occurred just proximal to the papilla of Vater in a woman, aged 59. The muscle coats are absent in the fundus of the sac which lies directly on pancreatic tissue, but muscle bundles are present about the plexus of ducts. This diverticulum was probably destined to be bilocular, the ducts resulting in the formation of a septum. The folding of the mucosa, as well as the tissue which contains Brunner's glands and lymph follicles, is unusual, and indicates an early stage in the formation of a diverticulum. van Gieson stain; × 7.

than 1 to 19 years, no cases; from 20 to 29 years, 1 case; from 30 to 39 years, 5 cases; from 40 to 49 years, 15 cases; from 50 to 59 years, 30 cases; from 60 to 69 years, 39 cases; from 70 to 79 years, 26 cases, and from 80 to 89 years, 6 cases. The youngest subject found to have

a duodenal diverticulum was 22 years of age. With the exception of some questionable cases in infants, this is the youngest subject with diverticulum found at necropsy that is recorded in the literature.

An analysis of the ages of the 14 persons who had multiple diverticula disclosed a distribution similar to that of the complete group. The duodenum which was found to have 5 definite diverticula was taken from a woman aged only 41 years.
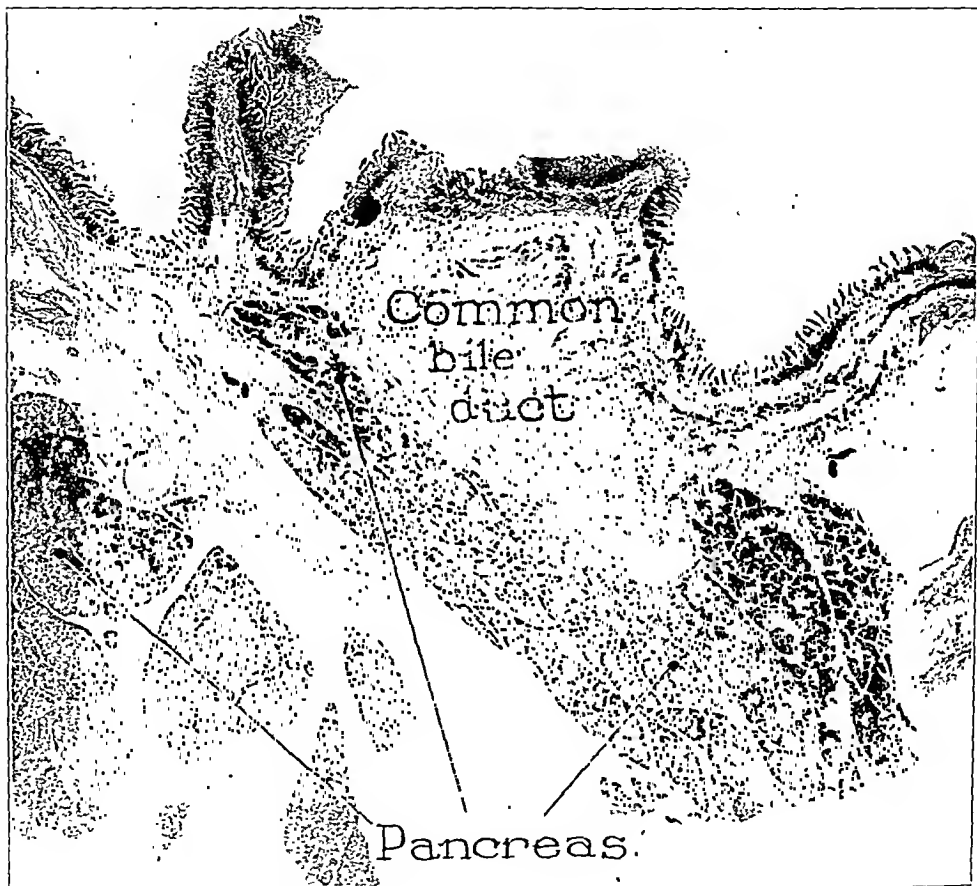
Fig. 5.—Normal duodenum, through the papilla of Vater, from a woman, aged 47. Pancreatic tissue is seen to extend upward to the mucosa, beside the common duct, leaving a small area devoid of muscle, where the mucosa lies immediately over the pancreas. van Gieson stain; × 7.

Of the 122 subjects with duodenal diverticula, 78 were men and 44 women.

In 34 (27.87 per cent) of the cases, there were diverticula of other portions of the gastro-intestinal tract. One was a diverticulum of the esophagus and 1, of the stomach; 2 were Meckel's diverticula; 8, jejunal and ileac diverticula other than Meckel's, and 24 sigmoid and other large intestinal diverticula. In 15 (12.3 per cent) of the cases there were

congenital anomalies, as follows: 2 cases of Meckel's diverticula; 1 case of accessory pancreas (situation not stated), 3 cases of accessory spleens, 1 case of aplasia of the left kidney, 1 case of cystic kidneys, 1 case of congenital cystic pancreas; 1 case of horseshoe kidney, 1 case of malformation of the spigelian lobe of the liver, 1 case of partial duplication of the left ureter, 1 case of a suprarenal rest in the kidney, 1 case of duplication of the gallbladder and 1 case of coarctation of the aorta and duplication of the left renal pelvis and ureter.

Fig. 6.—Cross-section through minor papilla and duct of Santorini, from a man, aged 47. Between the circular (a) and longitudinal (b) muscle layers, lie lobules of pancreas, while larger lobules lie beneath the mucosa and about the ducts. van Gieson stain; × 12.

Healed or chronic duodenal ulcer occurred in only 13 cases, and the average distance between the ampulla and pylorus was 7.6 cm. Cholelithiasis or cholecystitis or both were present in 39 cases (31.96 per cent).

In an attempt to find evidences of the precursors of these diverticula, a series of 80 apparently normal and fetal duodenums was studied. Fifty-eight blocks were cut from the region of the minor papilla, seventy-three blocks from the region of the major papilla and fifty-six blocks

from areas from 3 to 6 cm. distal to the major papilla. The entire duodenal wall and the underlying pancreas and connective tissue were included in all these blocks. The tissues were allowed to become fixed in a modified Kaiserling's solution before being cut, in order that the duodenal wall might better retain its relationship to the underlying tissues. The majority of sections were cut at right angles to the long axis of the duodenum, but some were cut parallel to the long axis. Occasional sections were stained with hematoxylin and eosin, but the majority were stained with van Gieson's stain, which gave clear distinction of muscle from connective tissue. Three series of serial sections were cut from the papilla of Vater and the adjacent duodenal wall and pancreas.
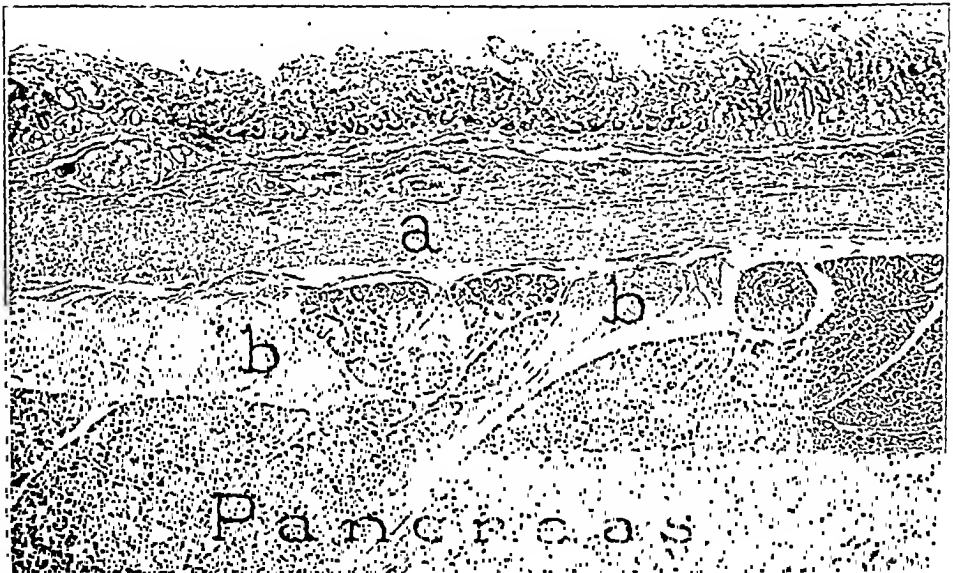
Fig. 7.—Section taken proximal to the papilla in a normal duodenum from a man, aged 37. In *a*, the circular muscle layer is intact, but in *b* pancreatic lobules have broken up the longitudinal muscles; × 25.

Because of the constant relationship of duodenal diverticula to the pancreas, and because of the fact that the duodenal musculature is absent from the diverticular walls, the sections were studied with special reference to the muscle layers and the underlying pancreatic tissue. In most of the blocks cut from the region of the ampulla (66 per cent), it was found that beneath the intramural portion of the common bile duct, just before it opens into the duodenum, the longitudinal layer was absent for a varying distance, although the circular muscle layer was usually intact. The longitudinal muscle layer, when absent beneath the duct, was usually seen to end by penetrating the subjacent pancreas. In the interval between the two ends of longitudinal muscle on either side,

the pancreas lay immediately beneath the circular muscle layer. Sections taken immediately distal to the tip of the papilla, in which case the ducts were not included in the sections, also frequently disclosed that the longitudinal muscle layer was absent for a short distance. However, in those sections taken more than 0.8 cm. distal to the tip of the papilla, both muscle layers were always found to be intact. Blocks which were
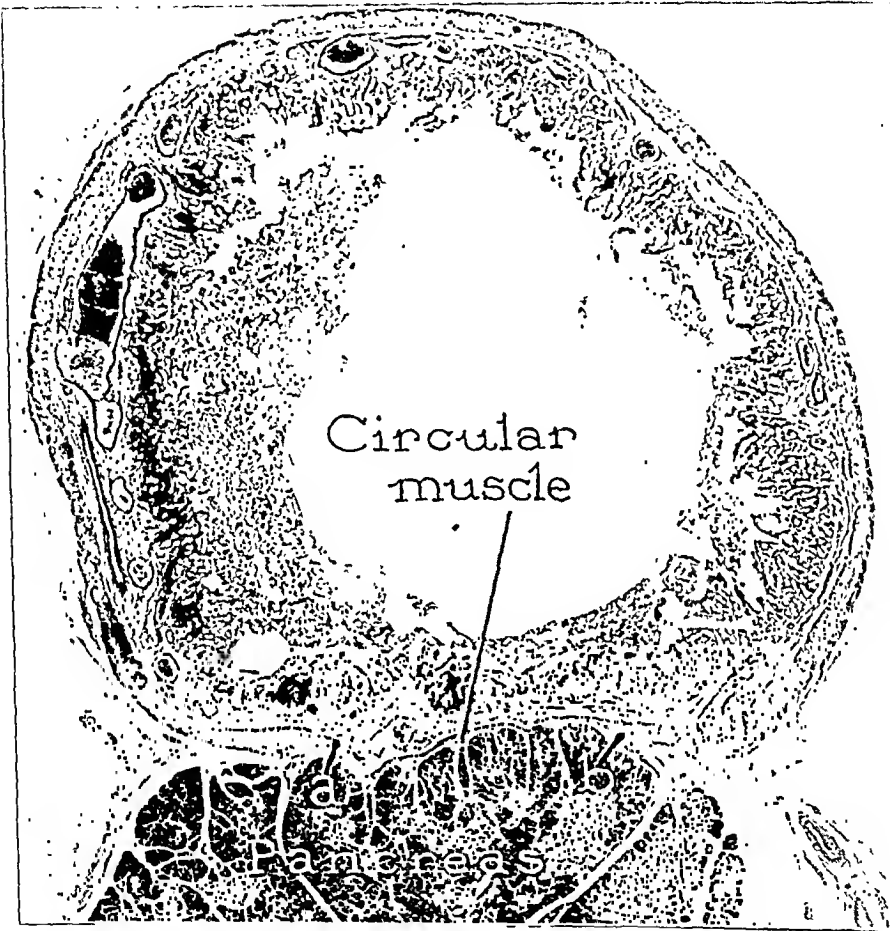
Fig. 8.—Cross-section through the duodenum of a fetus at full term. The circular muscle layer is intact, but at *a* and *b* the longitudinal muscle ends quite abruptly; × 15.

cut just at the point where the common bile duct penetrated the musculature revealed that both layers of muscle were absent where the duct lay, as was to be expected. In these sections it was frequently noted, however, that the longitudinal layer penetrated the pancreatic lobules a considerable distance before the circular muscle ended, either by an abrupt juncture with the musculature surrounding the ducts or by

also penetrating the pancreatic tissue. In a few instances a small lobule of pancreas was seen, lying between the ends of the two muscle layers and the musculature of the duct, immediately beneath the mucosa (fig. 5). In two cases there was pancreatic tissue about the duct beneath the mucosa. The finding of pancreatic tissue beneath the mucosa at the duct of Santorini is of common occurrence (fig. 6), but is seldom seen at the ampulla of Vater.

In a study of serial sections cut through the ampulla and the adjacent duodenal wall, the findings were similar to those just described. The

Summary of Results of Study of One Hundred and Twenty-Two Cases of Duodenal Diverticulosis

	Number	Per Cent
Cases of duodenal diverticula	122	
Cases of multiple duodenal diverticula....................................	14	11.47
Total number of duodenal diverticula.....................................	145	
Number associated with other diverticula of the gastro-intestinal tract.......	34	27.86
Position with relation to ampulla, ascertainable.............................	141	
At ampulla	82	58.15
Above ampulla	36	25.53
Below ampulla	23	16.31
Size:		
Diameter of orifice (average)..................................... 1.16 cm.		
Largest .... 5.00 cm.		
Smallest .... 0.20 cm.		
Depth of sac (average)... 2.03 cm.		
Largest .... 7.00 cm.		
Smallest .... 0.30 cm.		
Incidence by age:		
Average .... 60.8 years		
Oldest .... 87.0 years		
Youngest .... 22.0 years		
Sex:		
Men	78	64
Women	44	36
Associated with congenital anomalies	15	12.29
Associated with cholelithiasis or cholecystitis...........................	39	31.96
Associated with duodenal ulcer	13	10.65

circular muscle layer closed beneath the ducts, after they had penetrated the musculature, sooner than did the longitudinal layer, so that in part of the series only circular muscle was present beneath the ducts. To one side of the ampulla, the longitudinal muscle dipped into the pancreas before the ducts were reached, leaving only a thin band of circular muscle between the mucosa and the pancreatic lobules. The mucosa dipped down at this point, and lay close to the muscle, forming the rather deep depression which could be so commonly observed beside the ampulla. In sections cut through the tip of the ampulla, the circular muscle layer was markedly thickened in some areas close to the ducts.

In the region of the minor papilla, or ducts of Santorini, the longitudinal muscle was more frequently (82 per cent) displaced by pancreatic lobules, even in areas some distance away from the ducts (figs.

6 and 7). As has been mentioned, pancreatic lobules were frequently found lying about the plexus of ducts, beneath the mucosa, and in several instances masses of pancreatic tissue lay between or within the muscle layers (fig. 6).

The longitudinal and circular muscle layers were always found to be intact in those blocks cut varying distances distal to the papilla of Vater, except when the blocks were taken within 8 mm. of the papilla, in which case, as mentioned previously, the longitudinal layer was sometimes absent. In a few instances the muscle layers in the lower portions of the duodenum were definitely thinned and atrophic in appearance,

Fig. 9.—Cross-section through the duodenal wall and subjacent pancreas, from a fetus of 5 months. Between *a* and *b* pancreatic lobules have displaced both circular and longitudinal layers. On the left, the longitudinal muscle is seen to dip down into the pancreas and connective tissue. van Gieson stain; reduced from × 45.

and in 4 cases some of the longitudinal muscle bundles were found to extend into the subjacent connective tissue and pancreas.

Sections from the duodenums of 10 fetuses, varying from 5 to 8 months in prenatal development, were studied. Variations in the musculature were found, similar to those just described in the adult. In five of eight blocks cut through the intramural portion of the common bile duct after it had penetrated the muscle layers and lay beneath the

mucosa, the longitudinal muscle was absent for a variable distance and was replaced by pancreatic tissue. In one instance there was a marked thickening of the circular muscle layer close to the papilla. Of seven blocks cut from regions proximal to the major papilla, four contained areas in which the longitudinal muscle was absent and replaced by pancreas, which lay immediately beneath the circular muscle layer (fig. 8). At the points where the longitudinal muscle layers were interrupted, the muscle fibers dipped down beneath the pancreatic lobules. In a fetus of 5 months' development, the pancreas was found to have penetrated the circular as well as the longitudinal muscle layer, in an area proximal to the papilla of Vater (fig. 9).

<div align="center">COMMENT</div>

From the results of this study, an estimate of the incidence of duodenal diverticula could be only roughly approximated. As is well known, when one becomes interested in a particular lesion and begins to search diligently for it, it will be found more frequently than when casual observation of the organ in question is made. This point is brought out by the increased frequency with which duodenal diverticula have been found at the Mayo Clinic within the last few years. Thus, in 1913, 1914, 1915 and 1918, only 1 duodenal diverticulum was found each year, while in 1916, 1917, 1919 and 1920, none was recorded. In 1921, 3 cases were recorded; in 1922, 5, etc. The incidence then gradually increased each year with the exception of 1926; in 1930 the maximum of 2.8 per cent among all postmortem examinations was reached. However, up to June 1, 1931, in the course of 216 abdominal examinations, duodenal diverticula were found in 11, or in more than 5 per cent. Manifestly, since the majority of postmortem examinations at the Mayo Clinic are performed on adult bodies, these figures do not give an idea of the occurrence in a cross-section of the population. The same inaccuracy holds when one attempts to determine the incidence from the literature. Of the larger series of cases taken from records of necropsy, such as Linsmayer's series, the majority come from clinics where a large percentage of the examinations are performed on old subjects, and in these the incidence is higher. Reports from roentgenologists are also inaccurate, since very small diverticula cannot be detected by them, and in addition, they see primarily adults, persons with gastro-intestinal complaints. From various sources then, by rough estimation, the incidence among all persons is perhaps less than 1 per cent, although even this figure seems high if compared with Rankin and Brown's [58] estimate, which is less than 1 per cent for diverticulosis of the entire gastro-intestinal tract.

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58. Rankin, F. W., and Brown, P. W.: Diverticulitis of the Colon, Surg., Gynec. & Obst. **50**:836 (May) 1930.

Compared with other diverticula of the alimentary tract, duodenal diverticula stand approximately midway between the most common and the least common. Diverticula of the colon, particularly of the sigmoid flexure, are by far the most common; Meckel's diverticula are said to stand second in frequency, while esophageal diverticula are said to be the most frequent of diverticula of the upper part of the gastro-intestinal tract. From our observations, we should estimate that duodenal diverticula are approximately as frequent in occurrence as are Meckel's diverticula, and more frequent in occurrence than esophageal diverticula. In the stomach and pharynx these anomalies are seldom found.

There has been considerable diversity in the terms used to designate duodenal diverticula. They are commonly referred to as "false" diverticula, this term being used in contradistinction to the "true" diverticula, the walls of which contain all the layers of the intestinal wall, as does a Meckel's diverticulum. "False" seems to us a misleading term, since duodenal diverticula are as truly diverticula as are Meckel's diverticula. Duodenal diverticula have also been termed "congenital" to distinguish them from the "acquired" diverticula associated with duodenal ulcer. This is erroneous, for in few of the cases have the diverticula been proved to be congenital. Odgers introduced the term "primary" to describe these diverticula, using "secondary" to describe the diverticula following ulcer. This is an improvement on the older term "false," but still does not seem satisfactory. The French term, *diverticules péri-vatériens,* is correct for those diverticula which occur beside the papilla of Vater, but is obviously incorrect when applied to those occurring in other situations. The old descriptive term used by von Rokitansky [59] with reference to most gastro-intestinal diverticula, namely, "mucosal hernias," is the only descriptive term which is entirely correct and which does not imply more than is accepted concerning these structures. It would seem that no descriptive adjective is necessary in describing these pouches, since "diverticulum" is now practically never used with reference to an ulcer crater or other pouching.

Practically all investigators of this subject are agreed that the walls of duodenal diverticula are made up of mucosa, muscularis mucosa and connective tissue, with occasional bundles of smooth muscle. Only a few exceptions to this statement have come to our knowledge in a review of the literature. Baldwin, in 1911, reported a series of cases and stated definitely that in all there was a layer of muscular tissue in the wall. Case and Bonneau [60] said that the smallest diverticula have muscle in

59. von Rokitansky, Carl: A Manual of Pathological Anatomy, London, Sydenham Soc., 1849-1854, vol. 2, p. 48.

60. Bonneau, Raymond: Diverticules du duodénum, Presse méd. **2**:817 (Sept. 26) 1923.

their walls, while those that are larger are devoid of muscle. Our study has shown that the small, early diverticula have the duodenal muscle coats extending for a variable distance down the sides of the diverticulum, but in no instance was a continuous layer of muscle found extending without break of continuity around the fundus of a diverticulum, as Baldwin described, and we could find no reports similar to Baldwin's in the literature. Our findings have corroborated the majority of the cases reported, in that the fundus of the diverticulum is usually devoid of muscle tissue or contains only a few, small, scattered fibers which can be identified by the van Gieson stain. The muscularis mucosa, as stated previously, was intact in all cases, and in a few instances seemed to be hypertrophied.

As stated by most authors, the mucosa is atrophic, smooth and thinned out in the large and obviously old diverticula. However, in those that are seen earlier in their development the mucosa frequently still retains a few folds and Brunner's glands, and an occasional lymph follicle (figs. 2, 3 and 4). In addition to the presence of mucosal folds and Brunner's glands, the early diverticula also have a different contour; they are either broad and shallow or deep and narrow, but they do not have the bottle-shaped outline of those that are older. This relatively small size of the orifice was emphasized by Linsmayer, who expressed the belief that the orifice retains approximately the size of the actual muscular defect, while the sac expands more and more with age and as pressure is exerted on its wall from within.

As to the histogenesis of these structures, the results of the study of normal duodenums can, we believe, be correlated with that of the structure of the diverticula. In human fetuses as well as in adults, we have found that pancreatic lobules frequently have developed in the position in which the muscle layers of the duodenum should normally develop (figs. 5, 6, 7, 8 and 9), and that this anomaly occurs most often in the region of the pancreatic ducts. It is well known that in embryonic life the epithelial elements of the gastro-intestinal tract, as well as of its offshoots, the liver, pancreas, etc., are well developed before the muscle layers of the adult tube are laid down. Lewis [48] stated that the dorsal and ventral pancreas have been found in 3 and 4 mm. embryos, and that the longitudinal muscle of the duodenum is not developed until the 75 mm. stage is reached, whereas Horton found circular but not longitudinal muscle in a 41 mm. embryo. In addition to the facts given, various investigators [51] have found that in some of the lowest vertebrates, pancreatic tissue is incorporated within the duodenal wall. All these facts, together with the fact that duodenal diverticula lie against the pancreas, without a muscular coat, seem to be convincing evidence that these diverticula arise on the basis of a *locus minoris resistentiae*

produced by an anomalous growth of pancreatic tissue in the wall of the duodenum. This anomaly may be a persistence of the condition found in some lower vertebrates.

The sequence of events may thus be somewhat as follows: The pancreas is laid down at an early fetal age, and the duodenal musculature develops later. If some pancreatic lobules have penetrated the mesenchyma in areas which were to have been occupied by the muscle layers, the muscle cells cannot develop in those areas. Gaps are therefore left in the muscle layer or layers. These gaps are small, but as age advances, or as increased pressure is brought to bear on the duodenal wall, or when the tissues have lost some of their elasticity, the mucosa is forced down through the muscle layers where they are thin or absent, and a diverticulum is formed. The gap in the muscle probably enlarges only slightly, and forms the neck of the sac. The mucosa, however, stretches out gradually, to form the bulbous sac which we see in the well developed diverticulum, while the pancreas gradually gives way to the advancing sac. If the sac continues to enlarge, it gradually pushes out beyond the confines of the pancreas, and lies in the areolar tissue in that region, behind the peritoneum.

This explanation would hold for all the duodenal diverticula which we have examined. It explains their occasional occurrence in young persons as well as their greater frequency in older persons, and why they seem invariably to occur on the concave or pancreatic wall of the duodenum. It seems logical that growth of pancreatic tissue in the duodenal wall should be most likely to occur near the points where the pancreatic anlages first make their appearance as buds from the duodenal epithelium, thus explaining why most diverticula occur in the region of the pancreatic ducts. Linsmayer has emphasized these points particularly, and other investigators have mentioned the influence of accessory pancreatic tissue in weakening the wall of the intestine. One additional point in favor of this argument is the occasional occurrence of pancreatic tissue in the walls of ileac diverticula. Diverticula of the stomach, with accessory pancreatic tissue in their walls, have also been reported occasionally. Thus, although duodenal diverticula are not themselves congenital, the conditions which favor their development in later life are laid down in earliest fetal development.

This study has not substantiated the older and frequently quoted theory that diverticula occur at points of penetration of the duodenal wall by blood vessels. The blood supply of the second and third portions of the duodenum comes from the dorsal and ventral arcades formed by anastomosis of the superior and inferior pancreaticoduodenal arteries, which lie along the concave border of the duodenum, resting on the pancreatic head. Straight branches from these arches penetrate

4. At necropsy they are most frequently found in subjects who have passed the fifth decade of life, but they may occur in young subjects.

5. The large and obviously old sacs are bottle-shaped, while the early diverticula may be broad and shallow.

6. Duodenal diverticula are not congenital, but probably develop in adult life on the basis of a *locus minoris resistentiae* produced by an anomalous congenital growth of pancreas within the duodenal wall.

7. The wall of the apparently normal duodenum in the fetal and adult state may contain pancreatic lobules which displace muscle fibers, thus producing a *locus minoris resistentiae.*

8. Duodenal diverticula probably seldom cause clinical symptoms or serious complications, but it is possible that an unidentified pouch might form a serious hazard in the course of operation on the upper part of the abdomen.

9. The diverticula in this series were associated with congenital anomalies in 12.3 per cent of cases, and with other diverticula of the alimentary tract in 27.8 per cent.

UNILATERAL SPINE FUSION

A SIMPLIFIED TECHNIC

SAMUEL KLEINBERG, M.D.
NEW YORK

The operation of spine fusion is long past the experimental stage and is established as a valuable procedure in structural scoliosis, fracture of the spine, destructive disease of the vertebrae, spondylolisthesis and similar conditions. The operation is advised with reserve by many surgeons because the technic is difficult. In the hands of the experienced spine fusion may be accompanied by shock, which at times borders on being dangerous. It therefore occurred to me that it might be possible to circumvent these difficulties and yet attain the primary object of the operation, namely, fusion of the laminae and spinous processes, by employing a simplified technic. The idea originally grew out of my experience in scoliosis. In the very severe types of this deformity one is compelled to do a unilateral fusion, as it is frequently difficult, and sometimes impossible, to expose thoroughly the posterior arches on the convex side of the curve. In many cases the apparently incomplete operation was entirely satisfactory. Unilateral spine fusion, according to the method about to be described, is especially applicable to lesions of the spine in which there is little or no lateral distortion of the vertebrae, and to the lower half of the spine in which the spinous processes are fairly thick, that is, from the tenth dorsal to the sacrum.

TECHNIC

Let it be assumed that one is dealing with a case of tuberculosis of the first lumbar vertebra. A vertical incision is made in the median line of the back from the tenth dorsal to the third lumbar spinous process. The incision is extended through the superficial and deep fascia, immediately bringing into view the spinous processes (fig. 1). With a sharp thin chisel the eleventh dorsal spinous process is split in an anteroposterior direction; the left half is left attached to the vertebra, while the right half is split off from the lamina near its base. A periosteal elevator is inserted under the split off half of the process, and the process and the periosteum on the right side of the arch are elevated from the underlying bone to the articulation. The interspinous ligament is cut through in an anteroposterior direction, and the right half is retracted outward with a periosteal elevator. The same procedure is carried out on the other spinous processes and the interspinous ligaments. Within a few minutes and with little trauma the laminae on the right side of the

vertebrae are exposed. The retracted mass of tissue contains muscle, five large segments of bone, the corresponding interspinous ligaments and the periosteum of the laminae (fig. 2). Under this thick layer of tissue a graft of beef bone is placed on the laminae near the articulations (fig. 3). Frequently, before placement of the graft, chips of bone are removed from the laminae and placed across the interlaminar spaces. The sheet of muscle, bone and periosteum is then mobilized by two incisions through it, one at each extremity. With gentle traction the split portions of the spinous processes are brought into the interspinous areas and into contact with the unsplit segments (fig. 4). They are held in place with interrupted strong
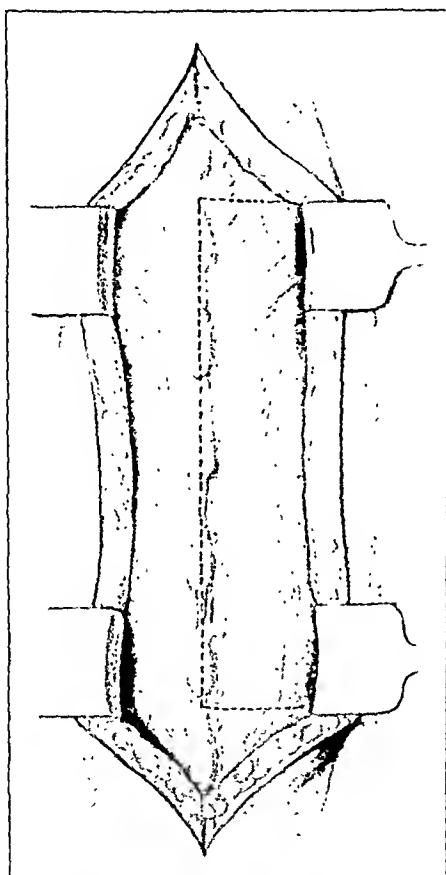
Fig. 1.—The vertical dotted line indicates the incision through the spinous processes and interspinous ligaments. The horizontal dotted lines indicate the incision through the periosteum to allow mobilization of the sheet of tissue containing the split off portions of the spinous processes, the periosteum, the interspinous ligaments and the muscles.

number 3 or 4 chromicized catgut sutures passed through the strong fibroperiosteal covering on the spinous processes. The wound is closed with a layer of catgut sutures for the deep fascia and another for the superficial fascia and a layer of silk sutures for the skin.

As the steps of the operation are few and the technic is simple, the actual operating time is rarely more than from fifteen to twenty

6 and 7). As has been mentioned, pancreatic lobules were frequently found lying about the plexus of ducts, beneath the mucosa, and in several instances masses of pancreatic tissue lay between or within the muscle layers (fig. 6).

The longitudinal and circular muscle layers were always found to be intact in those blocks cut varying distances distal to the papilla of Vater, except when the blocks were taken within 8 mm. of the papilla, in which case, as mentioned previously, the longitudinal layer was sometimes absent. In a few instances the muscle layers in the lower portions of the duodenum were definitely thinned and atrophic in appearance,

Fig. 9.—Cross-section through the duodenal wall and subjacent pancreas, from a fetus of 5 months. Between *a* and *b* pancreatic lobules have displaced both circular and longitudinal layers. On the left, the longitudinal muscle is seen to dip down into the pancreas and connective tissue. van Gieson stain; reduced from × 45.

and in 4 cases some of the longitudinal muscle bundles were found to extend into the subjacent connective tissue and pancreas.

Sections from the duodenums of 10 fetuses, varying from 5 to 8 months in prenatal development, were studied. Variations in the musculature were found, similar to those just described in the adult. In five of eight blocks cut through the intramural portion of the common bile duct after it had penetrated the muscle layers and lay beneath the

4. The patients have much less discomfort than from the more extensive operation of fusion.

5. Postoperative shock is eliminated by the short anesthesia and the simple technic.

6. Fusion occurs unusually fast because the spinous processes are brought into contact with segments of their own substance.
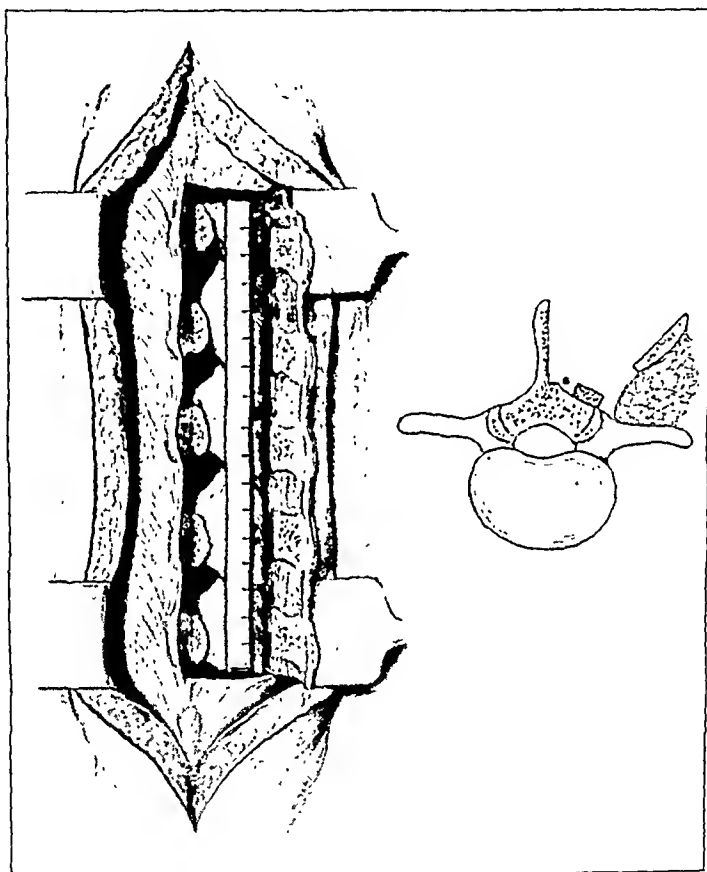
Fig. 3.—The same view as that shown in figure 2. A beef bone graft has been placed on the laminae covering the articulations. The small insert is a diagrammatic sketch showing half of the spinous processes split off and retracted outward with the periosteum and muscles. The small dark square represents a cross-section of the bone graft placed on the lamina near the intervertebral joint.

7. The ultimate support of the affected area of the spine comes from fusion both of the spinous processes and of the laminae.

As the spinous processes of the upper and middorsal vertebrae are comparatively thin, the operation of unilateral spine fusion is limited for the present to lesions in the lower half of the vertebral column, that is, from the ninth or tenth dorsal vertebra to the sacrum. In the

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already described. The total time of the operation was twenty-one and a half minutes, at the end of which time the patient was in excellent condition. The post-operative course was uneventful. Within two days the patient was entirely comfortable. He was discharged from the hospital at the end of seven weeks. A spinal brace was applied three months after the operation and discarded six months later, when support was no longer necessary. At the time of this report, one year after operation, the patient has no backache and can lift 100 pounds (45.4 Kg.) without much effort. In the roentgenographic lateral view of a lumbar spine that has not been operated on the spinous processes are separated by large distinct
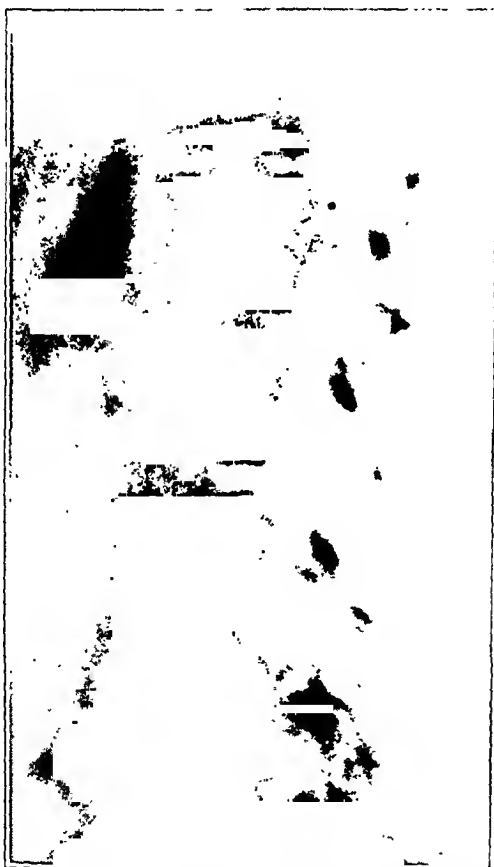
Fig. 5.—Lateral view of a normal lumbar spine. Note the clear interspinous spaces.

intervals (fig. 5). In the postoperative lateral view of this patient (fig. 6) one sees the darker shadows of the undisturbed portions (*a*) of the spinous processes, and between them are lighter shadows (*b*) of the displaced segments of bone bridging the interspinous areas. The body of the fractured vertebra is connected to the adjacent vertebral bodies by large bridges of bone. Thus the area of fracture is well protected by bony union of the injured vertebra to those above and below it both anteriorly and posteriorly.

CASE 2.—Joseph L., aged 55, had a fracture of the first lumbar vertebra. He was admitted to the Hospital for Ruptured and Crippled and was operated on on

produced by an anomalous growth of pancreatic tissue in the wall of the duodenum. This anomaly may be a persistence of the condition found in some lower vertebrates.

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similar operation was carried out lower down, including the fourth and fifth lumbar and the first and second sacral segments. The procedure was performed thoroughly, and yet the total time required for both operations was less than an hour. This patient, too, has done well. She is now walking about freely, wearing a spinal brace, and has no discomfort in her back.

CASE 4.—Miss K. R. was a patient of my associate, Dr. Buchman, who gave me the details in this case. For two years she had been suffering from tuberculous disease of the upper lumbar vertebrae. Psoas abscesses had developed. She had high fever for many weeks and was in poor general condition. The abscesses had to be drained. The patient was kept in bed on a convex frame for several months. Finally she improved sufficiently to warrant the undertaking of an operation. It was manifestly important to obtain fusion through an operation that would be thorough and yet of short duration and involve a minimum of trauma. The tenth dorsal to the fifth lumbar vertebrae, inclusive, were operated on. The technic described in this paper was used. The patient stood the operation well, and is convalescing satisfactorily.

SUMMARY

A simplified technic for spine fusion is described. Its chief advantages are simplicity and ease of execution.

The procedure of unilateral spine fusion permits thorough preparation of the vertebrae for fusion without removal of the bony support of the spinous processes. Union of the spinous processes is assured by bridging them with segments of their own substance. The time of operation is relatively short, and the manipulation is gentle. Hence this operation may be employed in patients of advanced age, and also in those who are debilitated and too sick to be subjected to prolonged anesthesia and severe operative procedures.

ADDITIONAL CASES.—During the six weeks preceding the writing of this report I used this technic in several additional cases in my service at the Hospital for Joint Diseases. One patient was a child of 7 years with tuberculous disease of the seventh dorsal vertebra. The fifth to the ninth dorsal vertebrae, inclusive, were operated on. Contrary to my expectations, I was able to employ the technic described. The only difficulty was the need for caution in splitting the spinous processes, which were very thin. The second case was in a girl of 15 years with moderate structural scoliosis. Fourteen vertebrae were operated on. The technic was carried out thoroughly, and the time of operation was fifty-six minutes. The patient was in good condition after the operation. During the last week I operated on a third patient, an adult suffering from tuberculosis of the third and fourth lumbar vertebrae. All of the lumbar vertebrae and the first sacral segment were fused. The operation, without any attempt at speed, was completed in a little more than thirty minutes.

PLASTIC OPERATIONS FOR INCONTINENCE OF URINE AND OF FECES

PHILIP B. PRICE, M.D.

TSINAN, CHINA

Incontinence of urine and feces are conditions so distressing to patients and offensive to their associates that it is not surprising that every conceivable method has been employed in attempts to relieve them. In that group of cases in which the incontinence is due simply to the sphincter having been cut across, accurate approximation of the divided ends usually results in complete restoration of function. Even when it has been divided in two or more places, or partially destroyed, operations which restore to use such muscle as remains, completing the ring with fibrous tissue of some sort, are often successful. But when the sphincter has been severely damaged, has been removed altogether, is congenitally absent or has had its nerve supply destroyed, the problem becomes far more difficult, and the prognosis correspondingly poorer. The multiplicity of operations devised only serves to show how earnest but vain has been the search for a satisfactory solution.

In 1927, Wreden of Leningrad attacked the problem of anal incontinence in a new way. He employed the contracting force of the gluteal muscles left in situ, transmitting this pull to the anus by means of strips of fascia, which act passively, much as a tendon does. He thus avoided the faults inherent in closed fibrous rings, and in transplanted strips of muscle, which sooner or later lose the power of contraction. He reported [1] one successful case in which he placed two loops of fascia lata subcutaneously, like interlocking links of a chain, the interlocking portions enclosing the anal orifice, and the lateral portions clasping a bundle of gluteal muscle fibers on either side. The pull of these two loops against each other produces the sphincter action. Dr. Harvey Stone [2] of Baltimore, using a slightly different technic, and prepared fascia instead of an autotransplant, has reported two cases, one of which was successful. Ransohoff [3] has also reported a successful case.

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1. Wreden, R. R.: A Method of Reconstructing a Voluntary Sphincter Ani, Arch. Surg. 18:841 (March) 1929.

2. Stone, H. B.: Plastic Operation for Anal Incontinence, Arch. Surg. 18:845 (March) 1929.

3. Ransohoff, J. L.: Wreden's Method of Reconstructing Voluntary Anal Control, Ann. Surg. 90:317, 1929.

A Chinese girl, with an unusual combination of congenital abnormalities, presented the double problem of incontinence of feces and urine, due to defective innervation. The operation of Wreden seemed particularly well adapted to the former, and accordingly was carried out.

REPORT OF A CASE

History.—Ma Mao, a Chinese girl, was first seen in the outpatient department in 1924. She was then 10 years old. The diagnosis at that time was: transposition of viscera and incontinence of urine and feces since birth. Admission to the hospital was advised, but since cure could not be guaranteed, she was taken away. During the following years large quantities of Chinese drugs were consumed, and various "old-time" treatments were endured in the effort to gain relief.

Examination.—On Nov. 26, 1930, she was brought again to the outpatient department. She was now 16 years of age, but looked not more than 13. Her height was 4 feet and 4 inches (132.1 cm.) and she was rather heavy-set. She appeared well nourished and in good health. Examination showed a true transposition of both thoracic and abdominal viscera. The breasts were small; the axillary and pubic hair was scanty. The clothing was wet with urine and soiled with feces. The skin of the perineum, buttocks and inner aspects of the thighs was excoriated and painful. The gluteal muscles were poorly developed. The anus was deeply depressed, and above and behind it, in the space normally occupied by the sacrum and coccyx there was a large hollow. The labia minora were elongated. The urethral meatus was in the normal position. Urine dribbled out constantly during examination. No vestige of the hymen could be seen. The vagina was surprisingly large and deep, but otherwise normal in appearance. In knee-chest posture the anal sphincter gaped widely, and then closed slowly and feebly. Digital examination showed a thin, weak, diaphragm-like external sphincter; the internal sphincter could not be made out. The rectal wall looked and felt normal.

The following day the patient was admitted to the University Hospital for study and treatment.

Routine work-up brought out some additional facts. The past history revealed that the patient had been in excellent general health; she had had measles in early childhood, had never had chronic constipation and for a year had menstruated regularly every four weeks without unusual discomfort. Physical examination showed one carious molar and pyorrhea; the heart (except for transposition) and lungs were normal. The tubes and left ovary were not definitely felt. The bladder (inspected through an open-air Kelly cystoscope) appeared normal, except that no sphincter action could be demonstrated on removal of the instrument. The legs were rather small, but strong. A chilblain ulcer was noted on the left foot. Systematic neurologic examination gave negative results except for unusually active knee reflexes. Laboratory examination of the urine revealed cloudiness, a trace of albumin; red blood cells, white blood cells and many bladder epithelial cells. Examination of the feces showed occult blood and many Ascaris eggs. There were 4,102,000 red blood cells, 80 per cent hemoglobin, 7,400 white blood cells and the differential count was normal. The Wassermann reaction was negative. Renal function (phenolsulphonphthalein intravenously) was 10 per cent the first, and 27 per cent the second, hour. Roentgenographic examination was made (figs. 1 to 7).

The diagnosis was: complete transposition of viscera; congenital absence of the coccyx and sacrum; congenital incontinence of urine and feces due to defective innervation; slight underdevelopment, general, sexual and mental; chronic low grade infection of the urinary tract; ascariasis; oral sepsis, and a chilblain ulcer on the foot.

The patient was kept under observation for four weeks. During this time her general condition improved markedly; she was rid of her intestinal parasites; the urine became normal; renal function rose to 86 per cent in two hours; the skin of the perineum and buttocks improved daily with nursing care and the liberal use of ointments; the oral sepsis and ulcer on the foot received attention, and there was

Fig. 1.—Roentgenogram of the chest, showing a true dextrocardia and gas in the stomach on the right. There are twelve thoracic vertebrae.

gain in weight. There was no appreciable improvement in the ability to control the urine or feces.

Operations and Course.—Wreden's operation was carried out on December 23 under ether anesthesia. The gluteal muscles were misshapen and small, probably due to the absence of sacrum and coccyx, so it was necessary to make the lateral incisions somewhat farther lateral and posterior than otherwise would have been necessary. When uncovered, the muscles appeared to be composed largely of fibrous tissue. Two strips of fascia, 19 cm. long, and 1 cm. wide, were cut from the right thigh. The remainder of the operation followed closely the technic suggested by Stone. It was sheer guess-work as to how tight to draw the interlocking loops. The operation itself was surprisingly easy. The anus assumed the usual puckered appearance, and through the anal walls the fascial loops felt much like a normal sphincter.

Fig. 2.—Roentgenogram showing the absence of the sacrum and coccyx. There are four lumbar vertebrae. The sacrum is represented by one large, irregularly-shaped vertebra.
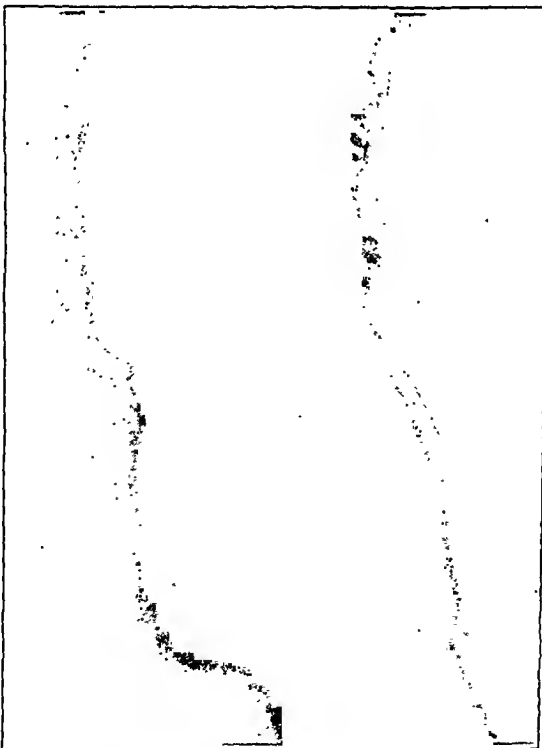
Fig. 3.—Lateral view of the pelvis, showing absence of the sacrum and coccyx.
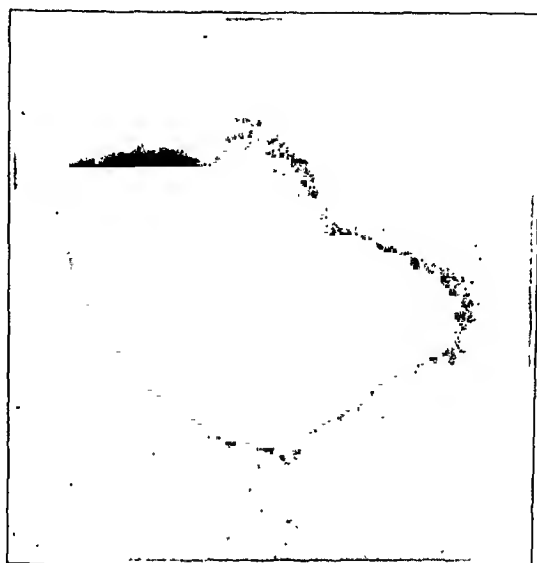
Fig. 4.—Roentgenogram taken after a barium meal, showing the fundus of the stomach on the right and the pylorus on the left.

Fig. 5.—Roentgenogram taken twenty-seven and a half hours after a barium meal. The barium is found in the cecum and ascending colon, which are situated near the midline, and in the transverse colon, which is shown running up to the splenic flexure in the right hypochondrium. A small amount of barium had been expelled from the rectum when this exposure was made.
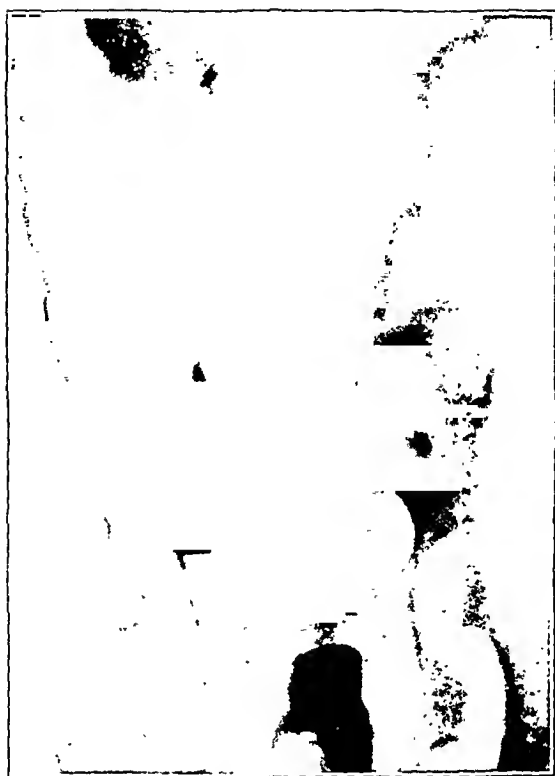
Fig. 6.—Roentgenogram taken after the injection of 800 cc. of barium emulsion into the rectum. The hepatic flexure is clearly shown. The shadow at the bottom is a barium-soaked cotton pad pressed against the incontinent anus.

Fig. 7.—Roentgenogram taken after an attempt to expel the enema.

Because of the constant leakage of urine, the wounds were covered with evaporated compound tincture of benzoin, and the patient was kept prone for five days. The incisions healed without the least inflammation. In the light of Stone's first experience, my colleagues and I decided to take advantage of this period and teach the patient to use her gluteals to keep her new "sphincter" closed. We failed in this.

On the eleventh day she was given liquid petrolatum and passed three controlled stools, greatly to her own surprise. Thereafter she had complete control of solid and semisolid feces. After vigorous catharsis, deliberately tried, there was some involuntary leakage of liquid feces. Figure 8 shows the record of defecations during three of the four weeks under observation. As will be seen, there was some tendency to constipation. Except for the incident just referred to, there was no leakage of feces during this period.

Encouraged by the apparent success of this operation, we sought by some similar means to relieve the incontinence of urine. It soon became evident, however, that the principle used in the first operation was not applicable to the urethra. Not only is the urethra so situated that interlocking loops of facia cannot very well be placed about it, but there are no available muscles on either
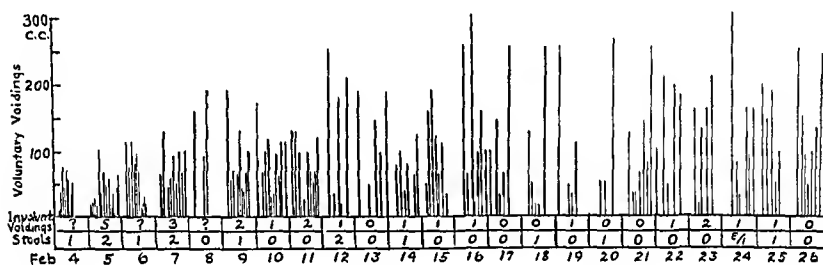
Fig 8.—Chart showing the number of controlled stools, the number of times urine was lost involuntarily, and the number and amounts of voluntary voidings, from the third to sixth postoperative week. A few voluntary voidings were thrown out, or were not measured separately, and so cannot be included. It will be noted that the largest amounts, as a rule, were passed the first thing in the morning.

side to which the lateral ends of the loops might be attached, except the muscles of the thighs, and here the movements of the legs would surely defeat the purpose of the operation. It occurred to us finally that voluntary constriction and relaxation might be obtained by fixing the distal end of a loop of fascia to a movable part of the body, so that the pull would be exerted, not by the contraction or elasticity of tissues so much as by the voluntary assumption of postures. For this purpose it was necessary to find some nearby portion of the body that in ordinary positions, such as standing and sitting, would be at a greater distance from the urethra, and in some extraordinary position, such as squatting or extreme flexion of the spine, would be nearer, and so relax the habitual tension on the fascial loop. After some experimenting, it was found that the rectus muscle a short distance above the symphysis most nearly fulfilled these conditions. The muscles were chosen rather than their fascia because of the inelasticity of the latter, which might subject the urethra to sudden, and possibly violent, pulls. It was decided, therefore, to attempt to sling a strip of fascia under the urethra near the bladder, with the two arms passing between the bladder and symphysis upward to be attached to the rectus muscle on either side.

Before operation a careful cystoscopy was done. The bladder mucosa was found to be normal everywhere. The urethral orifices appeared normal, and urine could be seen coming from them in normal spurts. A sense of fulness was produced by distending the bladder with 100 cc. of fluid, and this fluid could be expressed by the patient with a force exceeding the weight of 30 cc. of water. We concluded that in size, sensation and muscular power the bladder was potentially normal.

Operation was performed on Jan. 16, 1931, under ether anesthesia. One hundred cubic centimeters of air was injected into the bladder, the rubber catheter being clamped and left in place. The patient was placed in Edebohl's lithotomy position. A strip of fascia as long as could be obtained (19.5 cm.) and 2 cm. wide was taken from the the left thigh. An 8 cm. incision was then made above the symphysis pubis, the recti exposed on either side, and freed from their fascia medially. The peritoneum was rubbed off the anterior surface of the bladder out of harm's way. It was relatively easy to push the bladder away from the symphysis and expose the roof of the urethra; but when we attempted to pass an instrument under the urethra and up on the other side, it proved surprisingly difficult. None of our instruments seemed to be the right size or shape. First I tried, with one hand in the wound and the other under the sheets in the vagina, to direct the point of an aneurysm needle between the urethral and vaginal walls at a point about half way between the urethral orifice and neck of the bladder, an assistant manipulating the handle. Between us the instrument slipped somewhat out of place, and the bladder was perforated near the midline posteriorly, with escape of air and urine. The bladder had to be subjected to a wide dissection in order to close this hole satisfactorily. With this improved exposure, working from above, I was finally able to pass the aneurysm needle under the urethra, a little nearer the distal end of the canal than I had originally planned. A nurse with a finger in the vagina helped to prevent perforation of its mucosa. A piece of strong catgut was pulled through this tract, and in turn the strip of fascia (fig. 9). Because the fascial strip was not as long as we could have wished, the end of each arm was split into two fingers, and these were fastened around a generous portion of rectus muscle on either side, 5 cm. above the upper border of the symphysis. It was then found that the bladder tended to herniate between the easily spread arms of the V; otherwise the suspended fascia would prevent the anterior wall of the bladder from approaching the inner surface of the pubes, and thus create a dead space. Therefore, we sewed the muscles together behind the transplanted fascia (fig. 10). The ends of the sling were drawn up and fastened tight enough to prevent the rubber catheter from being withdrawn readily. The upper portion of the sling lay between the recti, and did not come in contact with the sheath, which was closed anterior to it. A small celluloid-tissue drain was put in the lower angle of the wound.

The catheter was left in the bladder, but it did not drain well; the following day the end of it was found in the vagina. So the patient was put in Fowler's position with the knees well flexed. In this position there was free discharge of urine, and we were dubious about the success of the operation. There was low grade fever for a week. The suprapubic wound became infected, and the discharge showed a pure culture of B. coli. Two-hourly irrigations of the wound with saturated boric acid solution through a Carrel tube brought about rapid improvement, the bacterial count dropping from 18 to zero in a few days.

The patient was allowed to walk on the fifteenth day, and the nursing staff undertook to train her to control her urine. For two or three days she was kept in the toilet, and urged to respond immediately to every slight impulse to urinate.

As soon as she learned that it was possible for her to go a whole day without wetting herself, she became interested in the training and made rapid progress. She learned the difference between sitting with and without flexing the spine. Figure 8 shows the improvement in control during the first three weeks of this training. The largest single amount voided was 350 cc. on the day of her discharge, March 6, forty-six days after operation. More than once she was able to go through a whole night without voiding. But her control was not perfect at the
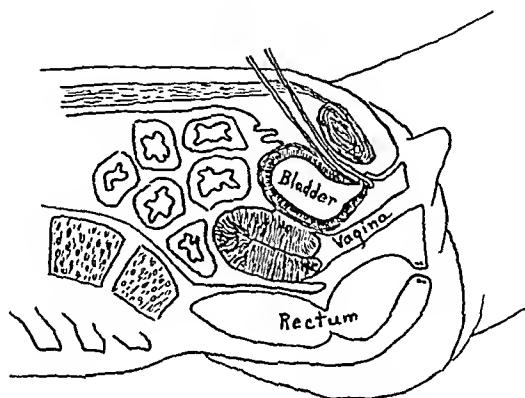
Fig. 9.—Schematic drawing of the pelvis in longitudinal section, showing the fascial sling placed about the neck of the bladder, and between the symphysis and anterior wall of the bladder.
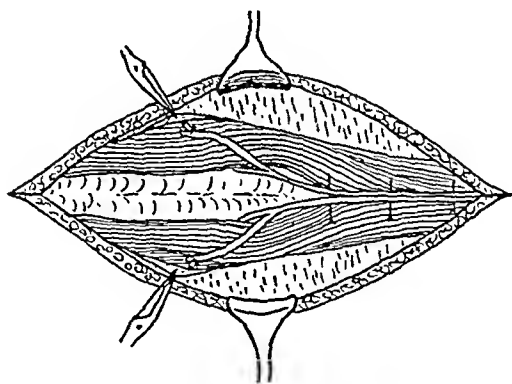
Fig. 10.—Showing the ends of the strip of fascia attached to the rectus muscle on either side, and the approximation of the muscles behind the fascial sling.

time of her discharge. Accidents still occurred every day or two, sometimes at night, sometimes because she indulged in the habit of squatting on her haunches to rest herself, and once or twice because of emotional upsets.

Examination on the day of discharge showed all the wounds thoroughly healed. The new anal "sphincter" felt much like a normal tight sphincter, but could be dilated widely without pain. The patient could not relax it voluntarily. The skin of the perineum was normal. In the anterior vaginal wall the fascial sling could be felt, and its position seen, about 1 cm. from the urethral meatus. On flexing and extending the spine, the cord of fascia could be felt to move slightly.

The patient was readmitted for observation on June 4, 1931, five and a half months after her first, and four and a half months after her second, operation. She complained of slight leakage of urine at times, and of pain when the bladder was full, just before, but not during micturation. Her general condition was excellent. The operative scars were healthy; there was slight keloid formation. The fascial transplants felt and acted much the same as on her discharge three months before. The urine was found strongly alkaline with a few pus cells. Cystoscopic examination showed a rather spastic bladder, mildly inflamed at the trigone, but otherwise normal. Renal function was 32 and 18 per cent (total 50 per cent) in two hours. The feces were normal. Leakage of urine was found to be due to carelessness in posture. With some additional coaching, and change of reaction of the urine, there was no further leakage or discomfort, even though the fluid intake was increased to over 3,000 cc. a day. The largest single amount voided was 380 cc. There was no leakage of feces during the six days of observation.

The patient has been followed for over a year, and her control of both urine and feces remains satisfactory.

COMMENT

Congenital absence of the terminal nine or ten segments of the spinal column is an exceedingly rare anomaly. So far we have not been able to find in the literature any reference to a similar condition. Transposition of viscera is doubtless more common among the Chinese than the four reported cases (Fay [4]) would indicate. The case reported here is the fifth.

By definition, a sphincter is a ring of muscle closing an orifice. The term cannot rightly be applied, therefore, either to Wreden's mechanism, or to the one we have described, for they are neither rings nor muscles.

Both in this case and in a subsequent one, we have shared Stone's difficulty in teaching the patient to tighten voluntarily the interlocking loops of fascia about the anus. Moreover, as my colleague Dr. L. M. Ingle has pointed out, contraction of the gluteal muscles brings them nearer the midline and would tend to relax rather than tighten the fascial loops; i. e., the patient might conceivably learn to relax the "sphincter" to some extent, but could not possibly tighten it by any direct muscular action. We believe, therefore, that this ingenious and successful mechanism is not, strictly speaking, voluntary, but that it forms a permanently elastic constriction about the anus, which is sufficient under ordinary conditions to prevent leakage of feces, but which yields to the expulsive force of peristalsis during defecation, without any voluntary relaxation on the part of the patient.

On the other hand, the mechanism which we devised for incontinence of urine in the case just described is truly voluntary.

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4. Fay, T. D.: Report of a Case of Complete Transposition of Thoracic and Abdominal Viscera, Chinese M. J. **46**:318, 1932.

SUMMARY

A Chinese girl, with transposition of thoracic and abdominal viscera and congenital absence of sacrum and coccyx, the latter an exceedingly rare condition, presented problems of complete incontinence of feces and urine, due probably to defective innervation.

Wreden's operation was successfully used to relieve the anal incontinence.

For relief of the urinary incontinence, a method was devised which utilizes bodily posture to tighten or relax a strip of fascia slung about the urethra. In this case it has resulted in voluntary control of the bladder. Details of the operation are given.

The results of the two operations after a period of over a year have been satisfactory.

GYNECOMASTIA

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Gynecomastia, derived from the Greek words: gyne, woman, and mastos, breast, has been a recognized entity since the days of Aristotle,[1] who reported that he had examined several such anomalies. The surgical removal for tumefaction of the breast was first advised by Paulus Aegineta[2] in 1556. He was followed by such men as Haly Abbas[3] and Abul-Casimir el Zahrawi.[4] In 1880, Olphan[5] wrote an interesting article on gynecomastia. Schuchardt,[6] in 1884-1885, reviewed the literature for new tissue formation in the male breast and from his findings published three papers. Two of these dealt with pathologic conditions, while the third described 40 cases as examples of true gynecomastia. Gruber,[7] in 1886, concluded that true gynecomastia was a physiologic phenomenon with all the characteristics of the female organ. Schuchardt,[6] however, included mastitis in his classification.

Gruber,[7] Langer,[8] Luschka[9] and Momberger[10] were some of the first to study the gross and microscopic anatomy of the breast. They

1. Aristotle: Hist. Animal (Parisiis), 1542, Calvarini, lib. III, chap. XX.

2. Paulus Aegineta: Medicinae totius enchiridion septem libris universam recte medendi rationem complectus, Opera Basileae, 1556, lib. VI, chap. XLVI, p. 225.

3. Haly Abbas: Liber totius medicine necessaria continens, Lugduni, J. Myteructe, 1523.

4. Abul-Casimir el Zahrawi: Tractatus de operantine manus arabice et latine cura, Oxford, J. Channing, 1778.

5. Olphan, H.: Un mot sur la gynécomastie, ou hypertrophie mammaire chez l'homme, Thèse de Paris, 1880, no. 159.

6. Schuchardt, B.: Zur Casuistik und Statistik der Neubildungen in der männlichen Brust, Arch. f. klin. Chir. **31**:1, 1844; Weitere Mittheilungen zur Casuistik und Statistik der Neubildungen in der männlichen Brust, ibid. **32**:227, 1885; Ueber die Vergrösserung der männlichen Brust, ibid. **31**:59, 1885.

7. Gruber, W.: Ueber die männliche Brustdrüse und über die Gynäcomastie, Mem. Acad. imp. d. sc. de St. Petersburg **10**:1, 1886.

8. Langer, C.: Ueber den Bau und die Entwicklung der Milchdrüse bei den Geschlechtern, Deukschriften d. Kais. akad. d. Wissenchaften math. Naturw. Klasse (Wien) **1**:402, 1852.

9. Luschka, H.: Die Anatomie der männlichen Brustdrüsen, Arch. f. anat. u. Physiol. u. Wissensch. **1**: 402, 1852.

10. Momberger, H.: Untersuchungen über Sitz, Gestalt und Färbung der Brustwarze nebst einigen Bemerkungen über die Contrationsfähigkeit des Warzenhofes und über die in demselben eingelagerten Talgdrüsen, Inaug. Dissert., Giessen, W. Keller, 1860.

maintained that although the mode of development, up to puberty, was essentially the same, the degree of enlargement was less in the male. Kölliker,[11] from his studies, stated that the formation of glandular tissue in the male is more extensive than in the nullipara of the same age. Stieda [12] considered gynecomastia as a hyperplasia of the normal tissues of the male, more marked in the connective tissue element.

Among the modern authors, Deaver and McFarland,[13] Hammett,[14] Kriss,[15] von Gusnar,[16] Steinach [17] and others have made valuable contributions to the literature on this subject.

The two conflicting theories of the causation of gynecomastia are the theory of Halban [18] and that of Herbst [19] and Steinach.[17] Halban [18] maintained that sex characteristics are unisexually determined at fertilization and that the gonads exercise only a protective influence over such characteristics. Herbst [19] and Steinach [17] believe that the anlage of the sex characteristics is bisexual and that the sex hormone has a specific as well as an antagonistic effect.

However, the nature of gynecomastia and the factors entering into the production of this abnormality in the male breast are not clearly understood. One of the reasons for this obscurity is undoubtedly the variety of forms which this disease may take and the multiple conditions which may be associated with it. Much of the confusion has resulted from a failure to define clearly the limits of gynecomastia. The assumption of many authors that mere enlargement in the region of the male breast is synonymous with abnormal physiologic hypertrophy

11. Kölliker, cited by Schaumann, H.: Beitrag zur Kenntnis der Gynäcomastie, Verhandl. der phys.-med. Gesellsch. zu Würzburg **28**:1, 1894.

12. Stieda, H.: Beitrag zur histologischen Kenntnis der sogenannten Gynäkomastie, Beitr. z. klin. Chir. **14**:179, 1895.

13. Deaver, J. B., and McFarland, J.: The Breast; Its Anomalies, Its Diseases and Their Treatment, Philadelphia, P. Blakiston's Son & Company, 1917.

14. Hammett, F. S.: Gynecomastia, Endocrinology **4**:205, 1920.

15. Kriss, B.: Negation of Theory that Gynecomastia is Caused by Cessation of Inhibitory Action of Testicles on Mammary Gland, Arch. f. Gynäk. **141**:503, 1930.

16. von Gusnar, K.: Histologic Study of Male Mammary Glands with Explanation of Certain Pathologic Changes, Arch. f. klin. Chir. **153**:253, 1928.

17. Steinach, E.: Willkürliche Umwandlung von Saügetiermannchen in Tiere mit angeprägt weiblichen Geschlechtscharakteren und weiblichen Psyche, Arch. f. d. ges. Physiol. **144**:71, 1912; Geschlechlstrieb und echt sekundäre Geschlechlsmerkmale als Folge der innersekretorischen Funktion der Keimdrüsen, Zentralbl. f. Physiol. **24**:551, 1910.

18. Halban, J.: Die innere Secretion von Ovarium und Placenta und ihre Bedeutung für die Function der Milchdrüse, Arch. f. Gynäk. **75**:353, 1905; Arch. f. Gynäk. **70**:205, 1902; Monatschr. f. Geburtsh. **53**:190, 1904; Arch. f. Gynäk. **114**:289, 1920; ibid. **130**:415, 1927.

19. Herbst, C.: Formative Reize in der tierischen Ontogenese, Leipzig, A. Georgi, 1901.

has also added to the problem. It is therefore necessary to point out that various neoplasms producing enlargement in the tissue surrounding the male nipple have been needlessly included in the discussion.

In general, gynecomastia is the result of (1) general and of (2) local factors. Among the general factors are: (*a*) A lack of sex differentiation in the sex organs (bisexuality). Here the female factor predominates. (*b*) A lack of the male sexual influence where the male factor is lessened and other endocrine disturbances influencing by stimulation or inhibition the male or female hormone. Among the local factors are all local causes producing tumefaction of the male breast (trauma, mastitis, etc.).

GENERAL FACTORS

In support of the first classification, or the lack of sex differentiation in the sex organs, there is the work of Brambell,[20] who discovered ovarian tissue on the surface of the testes of pigs. There is also evidence that gynecomastia has been noted in hermaphrodism and pseudohermaphrodism. These facts are well illustrated by the case of von Humboldt, quoted by Haeckel,[21] of a solitary settler in a South American forest whose wife died at childbirth. In despair the man laid the child over his own breast, and the continued stimulus of suckling movements revived the activity of the mammary glands. Cases of castrated male sheep and goats suckling their offspring have been reported. Humboldt and Franklin [22] Schmetzer,[23] and others have cited examples of gynecomasts who have nursed infants. It may be interesting to note that infants have thrived on "witch's milk," although Schmetzer [23] emphasized that its composition is not that of pure milk. Chinagawayo, a Zulu chief, and a gynecomast at 55 years, had forty wives and over a hundred children, some of which he nursed himself.[24]

There are cases, however, which demonstrate that a gynecomast can have a normal libido. Pétrequin [25] reported a case in which the patient

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20. Brambell, F. W. R.: The Histology of an Hermaphrodite Pig, and Its Developmental Significance, J. Anat. **63**:397, 1929.

21. Haeckel, Ernst: The Evolution of Man, London, K. Paul, Trench & Co., 1883, p. 113.

22. Humboldt and Franklin, cited in Gould, G. M., and Pyle, W. L.: Anomalies and Curiosities of Medicine, Philadelphia, W. B. Saunders Company, 1897, p. 397.

23. Schmetzer: Milchabsonderung in männliche Brüsten, Schmidt's Jahrb. **15**:204, 1837.

24. Shufeldt, R. W.: Gynecomasty, with the Description of a Remarkable Case, Md. Council, Philadelphia **15**:244, 1910.

25. Pétrequin, H.: Existence de trois mamelles chez un homme qui devient père de cinq enfants trimammés, Gaz. méd. de Paris **5**:197, 1837.

(a man) married and proved his potency. Coe,[26] Paulicky [27] and others [28] reported cases of gynecomastia in which there was no evident abnormality of the genitalia and apparently no disturbance or defect in the sex organs. Pseudohermaphrodism, when the sex organs were imperfectly formed and the individual developed secondary female characteristics, was reported by Polaillon,[29] Dennis [30] and others.[31] Beau [32] and Luke [33] likewise cited cases in which gynecomastia was associated with imperfect development of the sex organs.

From the foregoing data the evidence indicates that the ovary and testicle coexist in the embryo, and that in certain cases, because of some developmental injury or anomaly, the testicle is not able to exert its normal inhibitory influence. When this action is withdrawn and the female hormone is inserted, as Steinach [17] demonstrated when he transplanted ovaries in castrated males, there is a tendency toward the formation of female characteristics. Likewise, Halban,[18] Kehrer,[34] Hegar,[35] and others have shown that in females, if the ovaries are removed, the mammae fail to develop, but if again implanted the mammae will resume their normal function. Foges [36] showed that the removal of ovaries, after puberty, leads to a termination of the menstrual cycle and an atrophy of the breasts.

In the second group of gynecomasts, the male sexual influences are lacking. These are the cases of gynecomastia associated with removal of the prostate or testicle or associated with testicular injury. Gynecomastia

26. Coe.: Ann. de gynec. **31**:456, 1889.

27. Paulicky: Deutsche mil.-ärztl. Ztschr., 1882, p. 222.

28. Foot: Remarks on Gynecomazia, Dublin Q. J. M. Sc. **41**:451, 1866; Gynecomastia in a Young Boy, M. Times & Gaz. **1**:11, 1860. Koster: Fall von Gynaekomastia unilateralis, München. med. Wchnschr. **52**:725, 1905. Morgan: Lancet **2**:767, 1875. Scheiber, S. H.: Hypertrophirte Brustdrüsen bei einen 45 jährigen Manne, Med. Jahrb., 1875, p. 261.

29. Polaillon: Sur un cas d'hermaphrodisme, Bull. Acad. de méd., Paris **25**:557, 1891.

30. Dennis, F. S.: System of Surgery, Philadelphia, Lea Brothers & Co., 1896, vol. 4, p. 942.

31. Chambers: Tr. Obst. Soc., London **21**:256, 1879. Kochenburger: Die Missbildung der weiblichen Genitalien; Casuistischer Beitrag, Ztschr. f. Geburtsch. u. Gynäk. **26**:73, 1893.

32. Beau: Gaz. d. hôp., 1849, p. 563.

33. Luke: M. Times & Gaz. **1**:11 (Jan. 7) 1860.

34. Kehrer, F. A.: Ueber gewisse synchrone nerven erscheinung und cycklische Vorgänge in den Genitalien und anderen Organen, Beitr. z. Geburtsh. u. Gynäk. **4**:228, 1901.

35. Hegar, A.: Korrelationen der Keimdrüsen und Geschlechtstimmung, Beitr. z. Geburtsh. u. Gynäk. **7**:201, 1905.

36. Foges, A.: Zur physiologischen Beziehung zwischen Mamma und Genitalien. Zentralbl. f. Physiol. **19**:233, 1905.

following prostatectomy was reported by Oppenheimer [37] and others.[38] Zeleneff [39] reported a right-sided orchidectomy with hypertrophy of the left breast in a youth 18 years of age. Tellgmann [40] cited a case in which the loss of the testes preceded the development of gynecomastia. Gynecomastia resulting from the disorders of secretion of the testicles has been reported by Bitny-Schliachto.[41] Bailey [42] called attention to the relationship between tumefaction of the mammary glands and mumps. Hassler [43] and others [44] have also reported such cases. Gynecomastia following trauma to the testicle has been recorded by Monaschkin.[45] He found that sections of the breast showed hypertrophy of the ducts, while those of the tumor showed embryonal cells. Gorham [46] and others [47] also reported cases in which atrophy of the testicle and gynecomastia followed trauma.

Simple atrophy of the testicle with gynecomastia has been pointed out by Gorringe [48] and others.[49]

37. Oppenheimer, R.: Gynäkomastie nach der Prostatektomie, Deutsche med. Wchnschr. **53**:883 (May 20) 1927.

38. Kondoleon, E.: Vergrösserung der Brustdrüse nach Prostatektomie, Zentralbl. f. Chir. **47**:1098, 1920. Mann, L. T.: Atrophies testiculaires et hypertrophies mammaires, Gaz. hebd. de méd. **14**:533, 1877. Petit de la Viléon: Cancer du sein chez l'homme, Bull. et mém. Soc. de chir. de Paris **20**:744 (Nov. 2) 1928.

39. Zeleneff, I. F.: Dextrolateral Castration in a Youth 18 Years Old: Hypertrophy of Left Breast, Russk. J. Kozhn. i. Ven. Boliezn., Moscow **23**:230, 1912.

40. Tellgmann: Unilateral Gynecomastia After Loss of Testis, Deutsche med. Wchnschr. **52**:2127 (Dec. 10) 1926.

41. Bitny-Schliachto, F. A.: Zur Frage Gynäkomastie, Virchows Arch. f. path. Anat. **269**:45, 1928.

42. Bailey, H.: Studies in the Male Breast, Lancet **1**:1258, 1924.

43. Hassler: Gynécomastie; Mastite chronique et adénite axillaire polyganglionnaire, Arch. de méd. et pharm. mil., Paris **23**:531, 1894.

44. Laubscher, B. J. F.: Abnormal Mammary Development in the Male, J. M. A. South Africa **3**:147 (Jan. 12) 1929. Lereboullet: Gaz. hebd. de méd. **14**:533, 1877.

45. Monaschkin, G. B.: Gynecomastia and Tumors of the Testis, Ztschr. f. Urol. **20**:8, 1926.

46. Gorham and Hare: Extraordinary Development of the Mammae in the Male, Lancet **2**:637, 1840; London M. Gaz. **2**:659, 1840.

47. Lacassagne: Gaz. hebd. de méd., 1877. Thomson, H.: Preternatural Enlargement of the Breasts in Man, Lancet **1**:356, 1837.

48. Gorringe, W. J.: Case of Injury to the Back with Subsequent Enlargement of the Mammae and Wasting of the Testes, Prov. M. J., London **10**:204, 1846.

49. Boerhaave: Tijdschr. van geneesk, 1838. Galliet: Gaz. méd. de Paris, 1850, p. 351; Sur deux cas de coincidance du développement anormal de la mammelle chez l'homme, avec une tumeur de l'épididyme, Compt. rend. Soc. de biol. **2**:36, 1850. Hutchinson, J.: Arch. Surg. **6**:155, 1895, plate 118; Gynaeco-

Orchitis and varicocele producing testicular atrophy and associated with gynecomastia were reported by Schmit [50] and Martel,[51] respectively. The association of varicocele with gynecomastia was found in one case of the present series (P. N. 38637). Galliet [52] reported a case of gynecomastia following a tumor of the epididymis. In these cases the theory of Moszkowicz,[53] that testicular secretion inhibits the growth of the male breasts, is supported. An interesting case of a 19 year old boy suffering from gynecomastia for four years was reported by Schereschewsky.[54] He tells that a year previous to examination this patient was operated on for varicocele at which time a testicular graft, from a 40 year old man, was tried with no effect. The relationship between gynecomastia and chorio-epithelioma of the testis has been stressed and illustrated by case reports by Kriss [15] and others.[55] Gynecomastia developing in cases of teratoma of the testis was reported by Bailey [42] and Cairns.[56] Gynecomastia following sarcoma of the testicle was noted in one case of the present series (P. N. 37777). Erdheim,[57] after examining microscopically the breasts and testicles at autopsy, concluded that the etiology of gynecomastia is closely connected with the causation of sex characteristics and that it could not be attributed to one single factor.

mazia and Other Aberrations in the Development of Sex, ibid. **3**:327, 1891-1892. Laurent, E.: Les bisexués: Gynécomasties et hermaphrodites, Paris, G. Carré, 1894; De L'hérédité des gynécomastes, Ann. d'hyg. **24**:43, 1890. Lembert: Thèse de Paris, 1878; Gaz. hebd. méd., Sept. 14, 1877. Paulicky: Deutsche mil.-ärztl. Ztschr., 1882, p. 222. Weber, C.: Normiod ridge, Entwickelung beider Brust-drüsen bei Manne, Ztschr. d. deutsch. Chir. Ver. **5**:336, 1852.

50. Schmit, C.: Cong. franç. de Chir., Paris **6**:284, 1892; Deux cas de gynécomastie développés sans cause appréciable, Rec. de mém. de méd. mil., Paris **38**:690, 1881.

51. Martel: Hypertrophie du sein gauche chez un homme atteint de varicocèle du même côte, Arch. de méd. nav., Paris **60**:152, 1893.

52. Galliet: Sur deux cas de coincidance du développement anormal de la mamelle chez l'homme, avec une tumeur de l'épididyme, Compt. rend. Soc. de biol. **2**:36, 1850.

53. Moszkowicz, L.: Ueber den monatlichen Zyklus der Brustdrüse, Arch. f. klin. Chir. **142**:374, 1926.

54. Schereschewsky, N. A.: Sur la pathogénie et le traitement de la gynéco-mastie, Rev. franç. d'endocrinol. **6**:57, 1928.

55. Herzenberg, H.: Gynecomasty: Its Special Relation to Chorio-Epithelioma in Man, Virchows Arch. f. path. Anat. **263**:781, 1927. Prym, P.: Chorio-Epithelioma in a Man with Gynecomastia, Beitr. z. path. Anat. u. z. allg. Path. **85**:703 (Nov. 20) 1930.

56. Cairns, H. W. B.: Neoplasms of the Testicle, Lancet **1**:845 (April 24) 1926.

57. Erdheim, S.: Ueber Gynäkomastia, Deutsche Ztschr. f. Chir. **181**:208, 1928.

A thorough study on the relationship of the testicles to gynecomastia was made by Kriss,[15] who castrated twenty male guinea-pigs and afterward examined their breasts microscopically. In all of his cases he found no change in the glandular tissue. Further evidence that the testicles alone have little influence on gynecomastia was obtained by Stein and Herrmann,[58] who injected corpus luteum in castrated and noncastrated rabbits and found that both developed enlargement of the mammary glands. This work, however, only proves that the testicles, in themselves, are not the lone influence that prevents an enlargement of the mammary tissue. The testicles are closely connected to the intricate system of endocrine glands, and although they probably play the greatest part in sexual development, they function as a correlated part of the endocrine system.

The effects of other endocrine disturbances are shown by the association of gynecomastia with pituitary, suprarenal, cortical and thyroid disturbances.

The hypophyseal origin of Fröhlich's syndrome was definitely established by Cushing[59] and Ashner,[60] who demonstrated that obesity and genital hyperplasia developed in hypophysectomized animals. They also stated that the adiposity was caused by a deficiency of the posterior lobe. Cushing[59] explained that hyperplasia of the anterior lobe stimulates tissue growth, especially in the skeletal, cuticular and subcuticular tissues; conversely, when there is an insufficiency of the anterior lobe skeletal growth and sexual development are inhibited. Hyperplasia of the posterior lobe is associated with metabolism, for when this lobe is rendered inactive by disease or compression, metabolism is checked and an acquired high tolerance for carbohydrates permits the storage of fat.

Evidence of hypopituitarism, in a boy of 14 years, associated with mammary enlargement and small genitalia, was recorded by Gibson.[61] Among the evidence of hyperfunction of the anterior lobe, associated with mammary hypertrophy, is the report, by Roth,[62] of acromegalia in a man whose mammae secreted true milk. Hanel[63] described a case of a

58. Herrmann, E., and Stein, M.: Ueber künstliche Entwicklungschemmung männlicher sekundärer Geschlechtsmerkmale, Arch. f. Entwicklungsmechn. **48**:447, 1921.

59. Cushing, H.: Surgical Experiences with Pituitary Disorders, Weir Mitchell Lecture, J. A. M. A. **63**:1515, 1914.

60. Ashner, B.: Demonstrierte hypophysektomierte Hunde, Wien. klin. Wchnschr. **22**:1730, 1909.

61. Gibson, H. J. C.: Case of Exaggerated Gynecomastia, Edinburgh M. J. **30**:668, 1923.

62. Roth, O.: Auftreten von Milchsekretion bei einem an Akromegalie leidenden Patienten, Berl. klin. Wchnschr. **55**:305, 1918.

63. Hanel, H.: Mama lactans persistens masculina, Klin. Wchnschr. **5**:386, 1918.

43 year old man having possessed lactating breasts at 21 years, who later became the father of two normal children. Subsequent to his death, autopsy revealed a malignant disease of his hypophysis. Moehling [64] performed an operation on a 52 year old man who had developed gynecomastia in association with a pituitary adenoma. Mammary hypertrophy associated with attacks of chorea minor was noted by Weber.[65] Siegmund and Mahnert [66] demonstrated the effect of the anterior lobe hormone on the development of the sex glands in infants and fetuses. Intraperitoneal injections of an extract from the anterior lobe of the hypophysis, which were given by Putnam, Teel and Benedict,[67] produced an increase in the size of the nipples of a bulldog. This was also demonstrated by Frank and Unger (Scherschewsky [54]). Davidoff [68] called attention to a case of acromegalia in which lactation and menorrhagia had persisted for five years. A report from the woman's surgeon, who had performed a laparotomy two years previously, said that both ovaries were in a state of semi-atrophy with no signs of ovulation.

The concurrence of cirrhosis of the liver and gynecomastia, or tumors of the male breast, has been reported by d'Antona [69] and others.[70] This may be explained on the basis of a mild form of Wilson's disease (tetanoid chorea) in which there is a degeneration of the lenticular nucleus associated with hepatic cirrhosis. It is interesting to note that in d'Antona's case there was testicular atrophy.

There are cases in which the disturbance of the suprarenal cortex are associated with gynecomastia. Mathias,[71] at postmortem examination, described a carcinoma of the suprarenal cortex associated with

64. Moehling, R. C.: Pituitary Tumor Associated with Gynecomastia, Endocrinology **13**:529 (Nov.-Dec.) 1929.

65. Weber, F. P.: Notes on Mammary Enlargement, from Endocrine Disturbances in Males, M. Press **126**:425 (Nov. 21) 1928.

66. Siegmund, H., and Mahnert, A.: Effect of Hormone of Anterior Lobe of Infants and Fetuses on Development of Infantile Sex Glands, München. med. Wchnschr. **75**:1835 (Oct. 26) 1928.

67. Putnam, T. J.; Teel, H., and Benedict, E. B.: The Preparation of a Sterile Active Extract from the Anterior Lobe of the Hypophysis, Am. J. Physiol. **84**:157, 1928.

68. Davidoff, L. M.: Studies in Acromegaly, Endocrinology **10**:477, 1926.

69. d'Antona, L.: Hepatic Cirrhosis, Tumefaction of Male Mammary Glands and Testicular Atrophy, Policlinico (sez. prat.) **38**:261 (Feb. 23) 1931.

70. Paula, F.: Concurrence of Cirrhosis of the Liver and Gynecomastia; Four Cases, Deutsches Arch. f. klin. Med. **169**:83, 1930. Pellegrini, A.: Male Breast: Hypertrophy in Hepatic Cirrhosis, Semana méd. **1**:1108 (May 5) 1927. Tattoni, A.: Male Breast: Hypertrophy in Hepatic Cirrhosis, Morgagni **69**:1081 (July 10) 1927.

71. Mathias, E.: Ueber Geschwülste der Nebennierenrinde mit morphogenetischen Wirkungen. Virchows Arch. f. path. Anat. **236**:446, 1922.

mammary enlargement. Weber [72] recorded a similar case at a later date. A case of pseudohermaphrodism with suprarenal hyperplasia has been described by Brutschy.[73] Evidence that the injection of mammary extract producing a hypertrophy of the suprarenal gland and arrest in development of the testicle has been established by Spirito,[74] who, in addition, sanctions this extract in the treatment of Addison's disease.

A hyperthyroidosis accompanied by enlargement of the mamma was noted by Freeman.[75] At a later date, Alexander [76] called attention to a case of myxedema following mammary hypertrophy in childhood. In the present series, case P. N. 37676 was associated with hyperthyroidism. and P. N. 39356, with myxedema.

These cases clearly indicate the close relationship of the endocrine system to gynecomastia. A logical deduction indicates that the endocrine glands influence the male and female hormone activity by stimulation or retardation.

LOCAL FACTORS

Gynecomastia may be unilateral or bilateral, 87.2 per cent being unilateral and 12.8 per cent being bilateral. The hypertrophy which occurs may be caused by general or local factors or both. The local factors include some forms of chronic irritation which seem to create ideal conditions for the activation of cell growth. Although trauma has been associated with gynecomastia by Deaver and McFarland,[18] Léon [77] and others,[78] it occurs in only 14.5 per cent of the cases. It is questionable whether trauma plays any particular rôle in this phase of activity, although it is probably more closely associated with unilateral growth. The presence of some form of chronic irritation is suggested by the eosinophils and plasma cells in the peritubular, round cell infiltra-

72. Weber, F. P.: Cutaneous Striae, Purpura, High Blood Pressure, Amenorrhoea and Obesity of the Type Sometimes Connected with Cortical Tumors of the Adrenal Glands, Occurring in the Absence of Any Such Tumour, Brit. J. Dermat. **38**:1, 1926.

73. Brutschy, P.: Hochgradige Lipoidhyperplasie beider Nebennieren mit herdförmiger Kalkablagerung bei einen Fall von Hypospadiasis penis-scrotalis 'und doppelseitigem Kryptorchismus mit unechter akzessorischer Nebenniere am rechten Hoden, Frankfurt. Ztschr. f. Path. **24**:203, 1920.

74. Spirito, F.: Correlazioni fuzionali surrenomammare. Proposta di un nuovo metodo di cura del morbo di addison, Rassegna di clin., terap. e sc. aff. **22**:265, 1923.

75. Freeman, J. K.: Hyperthyroidosis Associated with Gynecomastia, Therap. Gaz. **40**:9, 1916.

76. Alexander, W.: Myxedema Following Mammary Hypertrophy in Childhood, Brit. M. J. **1**:349 (Feb. 23) 1929.

77. Léon: Arch. de méd. nav. Paris **31**:213, 1879.

78. Nélaton, A.: Gaz. d. hôp. **29**:126, 1856. Peters, D. C.: Hypertrophy of the Mammary Gland in a Soldier, Am. M. Times, N. Y. **6**:196, 1863.

tion, which is seen in practically every form of gynecomastia. Tenderness in 50 per cent of the cases also suggests a source of irritation. The round cell infiltration seen in gynecomastia has been explained by Dietrich [79] and Consten [80] as a resorptive process which may be similarly seen after physiologic hypertrophies and in the regressive phases of the female breast. However, the infiltration is often seen in hypertrophies of short duration before any evidence of resorption is noted. The presence of eosinophils and plasma cells is sometimes so marked that microscopically the hyperplasia simulates mastitis. In some cases
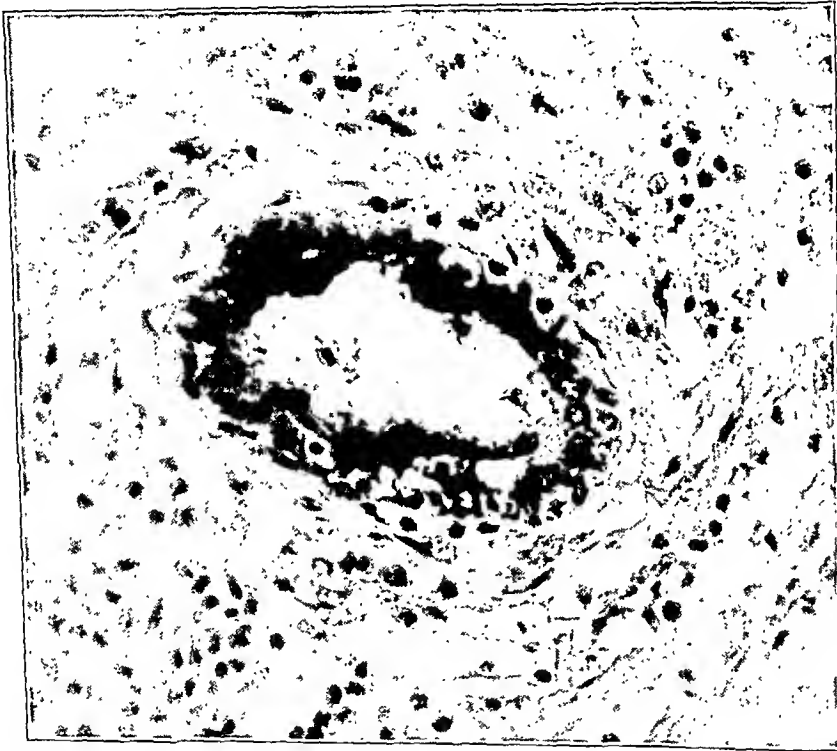
Fig. 1 (path. no. 41316).—Microscopic structure of tissues from a white youth, 17 years of age, who, for ten days, complained of a slightly painful tumor of his breast. The mass was excised and the patient is well two years later. The section shows epithelial hyperplasia surrounded by young fibroblasts interspersed with polymorphonuclear leukocytes, lymphoid and plasma cells. The section illustrates the association of hypertrophy with mastitis.

there is definitely an association with mastitis (fig. 1). Ciöffi [81] regarded tumefaction at the age of puberty in males as a temporary mastitis

79. Dietrich and Frangenheim: Neue Deutsche Chir. Stuttgart, Ferdinand Enke, 1926, vol. 35.

80. Consten, A.: Diffuse Fibromatosis of Mamma in Man, Deutsche Ztschr. f. Chir. **167**:264, 1921.

81. Ciöffi, A.: Tumori mammari maschile, Ann. ital. di chir. **9**:1147, 1930.

Gynecomastia

Path. No.	Age	Color	Symptoms	Duration, Months	Tumor	Location	Treatment	Microscopic Examination	Results
45537	42	C	......	.	Unilateral; discrete	......	Excision of breast	Fibrous hyperplasia	
45411	43	C	Disappearing, painless lump	24	Unilateral; discrete	Right	Excision of tumor	Fibrous hyperplasia; atrophy of duct cell	
44224	23	W	Trauma; mass, tender; gradual growth	36	Unilateral; discrete	Left	X-rays, nine exposures; excision of tumor one year later	Duct and marked fibrous hyperplasia (stroma)	Well 1 yr. later
43911	..	..	......	.	....	......	Amputation of breast	Duct and fibrous hyperplasia (stroma)	Lost 3 yrs. later
42730	9	..	Gradual enlargement, tender	1½	Unilateral; discrete	......	Excision of tumor	Fibrous and marked duct hyperplasia (periductal)	Well 1 yr. later
42294	..	W	Trauma; slow growing mass	1½	Bilateral; discrete	Right and left	Complete excision of both breasts	Duct and fibrous hyperplasia	Well 2 yrs. later
42292	55	W	Tumor; rapid growth, tender	2	Unilateral; discrete	Left	Excision of tumor	Marked duct and fibrous hyperplasia (periductal)	Well 2 yrs. later
41925	12	W	Tumor; slow growth, painful	¾	Unilateral; discrete	Left	Excision of tumor	Duct and fibrous hyperplasia (periductal)	Well 4 yrs. later
41894	63	W	Trauma; tumor, slow growth; pain	1½	Unilateral; discrete	Left	Excision of left breast	Duct and fibrous hyperplasia (stroma)	Well 2 yrs. later
41657	34	C	....	.	....	......	Excision of breast	Duct and fibrous hyperplasia (stroma)	Lost 4 yrs. later
41316	17	W	Tumor; pain	½	Unilateral; discrete	......	Partial excision of tumor	Marked duct and fibrous hyperplasia (periductal)	Lost 2 yrs. later
41077	14	W	Trauma; tumor; pain	¾	Unilateral; discrete	Left	Excision of tumor	Marked duct and fibrous hyperplasia (periductal)	Lost 4 yrs. later
40668	67	W	Tumor; tender	1½	Unilateral; discrete	Right	Complete excision of breast; one roentgen treatment	Duct and marked fibrous hyperplasia (periductal)	Dead 1 yr. later; bladder inflammation
40630	62	W	Tumor; pain	2½	Unilateral; discrete	Right	Complete excision of breast; cautery	Duct and fibrous hyperplasia (periductal)	Well 3 yrs. later
39909	45	W	....	.	....	Left	Excision of breast	Duct and marked fibrous hyperplasia (periductal)	
39658	34	W	Tumor	.	Unilateral; diffuse	......	Excision of breast	Duct and marked fibrous hyperplasia (stroma)	Well 4 yrs. later
39619	44	W	Tenderness; tumor	4	Unilateral; discrete	Left	Roentgen treatment; excision of breast 1 month later	Fibrous hyperplasia (stroma); duct dilatation	Lost 5 yrs. later
38394	55	W	Tenderness; tumor	3	Unilateral; discrete	Left	Amputation of breast	Fibrous hyperplasia (stroma); duct cell atrophy	Well 1½ yrs. later
38356*	43	W	Tumor; pain	¾	Unilateral; discrete	Left	Excision of breast	Duct and fibrous hyperplasia (stroma)	Well 4 yrs. later (hypothyroidism)
38657*	20	C	Trauma; diffuse enlargement	96	Unilateral; diffuse; (one discrete nodule)	Left	Excision of tumor	Duct and fibrous hyperplasia (stroma); duct dilatation; Duct and fibrous hyperplasia	Lost 5 yrs. later

No.		History	Dur.	Type	Side	Operation	Pathology	Result
35487	W	Tumor; slow growth; painful	..	Unilateral; discrete	......	Excision of tumor	Duct and fibrous hyperplasia	Lost 5 yrs. later
33161	W	Pain; gradual swelling	2½	Unilateral; discrete	Right	Excision of tumor	Marked duct and fibrous hyperplasia (periductal)	Living 9 yrs. later (tuberculosis ?)
35777*	W	Tumor	1	Unilateral; discrete	Right	Excision of tumor	Marked duct and fibrous hyperplasia (periductal)	Well 6 yrs. later
35656*	W	Tumor; tender	2	Bilateral; discrete	Right and left	Excision of tumor masses	Duct and fibrous hyperplasia	Well 5 yrs. later
37493	W	Tumor; tender; slow growth	1½	Unilateral; discrete	Left	Excision of tumor	Duct and marked fibrous hyperplasia (periductal)	Lost 6 yrs. later
37379	W	Tumor; slow growth	5	Unilateral; discrete	Left	Excision of tumor	Marked duct and fibrous hyperplasia (stroma)	Lost 6 yrs. later
37203	W	Trauma; tumor; pain	4	Unilateral; discrete	Left	Excision of tumor	Duct and fibrous hyperplasia (periductal)	Well 6 yrs. later
37016	W	Tenderness; tumor slow growth	2½	Unilateral; (discrete); diffuse	Right	Complete excision of breast	Duct and marked fibrous hyperplasia (stroma); cystic dilatation	Well 6 yrs. later
37012	W	Bilateral enlargement	2	Bilateral; diffuse	Right and left	Bilateral, complete amputation	Duct and marked fibrous hyperplasia; cystic dilatation	Lost 6 yrs. later
36579	O	Tumor; slow growth; pain	12	Unilateral; multiple; discrete	Left	Amputation	Dense fibrous stroma	Lost 6 yrs. later
36506	:	Trauma; tumor; tender	1	Unilateral; discrete	Right	Complete excision of breast	Duct and fibrous hyperplasia; duct dilatation	Well 4 yrs. later
36144	O	Tumor; slow growth; pain	8	Unilateral; discrete	......	Excision of tumor	Duct and fibrous hyperplasia (stroma)	Well 7 yrs. later
36022	W	Tumor; gradual growth; pain	2	Unilateral; multiple	......	Complete amputation of breast	Duct and fibrous hyperplasia (stroma)	Well (lump in other breast) 1 yr. later
35910	:	....	..	Unilateral; diffuse; discrete nodules	......	Excision of tumor masses	Duct and fibrous hyperplasia (periductal)	Dead 1 yr. later
36768	W	Tumor; tender	1	Unilateral; discrete	Right	Complete excision of breast	Duct and marked fibrous hyperplasia (periductal)	Dead 5 yrs. later; generalized arthritis; no recurrence
35524	W	Tumor	3	Unilateral; discrete	Left	Complete excision of breast	Marked duct and fibrous hyperplasia	Well 7 yrs. later
35350	W	Tumor	3	Unilateral; discrete	......	Amputation of breast	Duct and fibrous hyperplasia (stroma)	Lost 7 yrs. later
33816	W	Tumor; short duration	..	Unilateral	Right	Excision of breast	Marked duct and fibrous hyperplasia (periductal)	Lost 7 yrs. later
32768	W	Tumor; slow growth; pain	7	Unilateral; diffuse	Right	X-ray, three series	(No operation)	Well 8 yrs. later; tumor disappeared
32274	W	Tumor	2	Unilateral	......	Excision of tumor	Duct and fibrous hyperplasia	Well 8 yrs. later; no recurrence
31965	O	Tumors; pain	..	Unilateral; multiple; discrete	Left	Excision of breast	Duct and marked fibrous hyperplasia (stroma)	Lost 9 yrs. later
31661	W	Tumor	3	Unilateral; discrete	Left	Excision of tumor	Fibrous hyperplasia; duct dilatation	Lost 8 yrs. later
31660	W	Pain; tumor	3	Unilateral; discrete	Left	Excision of tumor	Fibrous hyperplasia; duct dilatation	Lost 8 yrs. later

* The case was complicated by one of the following conditions: hyperthyroidism, hypothyroidism, varicocele and carcinoma of the testicle.

Gynecomastia—Continued

Path. No.	Age	Color	Symptoms	Duration, Months	Tumor	Location	Treatment	Microscopic Examination	Results
30834	65	W	Pain; tumor	2	Bilateral; diffuse; (one discrete nodule)	Right and left	Bilateral amputation of breast	Duct and fibrous hyperplasia	Died 5 yrs. later
30542	68	W	Tumor	3	Unilateral; diffuse	Left	Complete excision of breast	Duct and fibrous hyperplasia	Well 8 yrs. later
30510	15	W	Tumor	1	Unilateral; discrete	Left	Excision of breast	Duct and fibrous hyperplasia	Well 9 yrs. later; no recurrence
30218	..	W	Nipple irritation	1½	Unilateral	......	Excision of nipple and areola	Duct and fibrous hyperplasia (stroma)	Dead 5 yrs. later
29114	20	W	Tenderness; tumor	24	Unilateral; multiple and discrete	Right	Observed	....	Well 10½ yrs. later; no change in tumor mass
29925	74	W	Burning; tumor	3	Unilateral; discrete (similar mass in opposite breast 5 yrs. later)	Right	Excision of tumor; excision of second tumor 5 yrs. later	Fibrous hyperplasia; duct hyperplasia with dilatation	Dead 3 yrs. later; heart trouble
28910	..	W	Tumor; tender	..	Unilateral; discrete	......	Excision of tumor	Duct and marked fibrous hyperplasia (periductal)	Lost 9 yrs. later
24503	26	W	Tumor; both breasts; tenderness	36	Bilateral; discrete	Right and left	Observed; later, amputation of right breast	Dense fibrous stroma	Lost 10 yrs. later
24624	22	W	Trauma; tumor	72	Unilateral; diffuse; discrete nodule	Right	Excision of breast	Duct and fibrous hyperplasia (periductal)	Well 12 yrs. later; no recurrences
24617	48	W	Yellow discharge; tumor; slow growth	36	Unilateral; discrete	Right	Excision of breast; cautery	Papillomatous duct hyperplasia	Well 8 yrs. later
24430	16	W	Tumor; pain	2	Unilateral; discrete	Right	Excision of breast	Marked duct and fibrous hyperplasia	Well 11 yrs. later
24174	36	W	Trauma; tumor	12 yrs.	Unilateral; discrete	Right	Excision of breast	Dense fibrous stroma	Well 12 yrs. later
23301	68	W	Tumor; slow growth	7	Unilateral; discrete	Right	Excision of tumor	Duct and fibrous hyperplasia (stroma)	Well 13 yrs. later
23500	33	C	Tumor; pain	36	Unilateral; discrete	Left	Excision of breast	Duct hyperplasia (papilloma)	Lost 13 yrs. later
22192	39	W	Tumor; pain	..	Unilateral; diffuse	......	Amputation of breast	Duct and marked fibrous hyperplasia (periductal)	Lost 14 yrs. later
20499	72	W	Tumor	..	Unilateral; discrete	Left	Excision of tumor	Duct and fibrous hyperplasia	Dead 3 yrs. later; heart failure
14074	33	W	Tumor; hemorrhagic discharge	46	Unilateral; discrete	Right	Excision of tumor	Duct hyperplasia (papillomatous)	Lost
13023	54	W	Tumor	2	Unilateral; discrete	Left	Excision of breast	Duct and fibrous hyperplasia (stroma)	Dead 10 yrs. later; pneumonia
12380	40	W	Itching; tumor	3½	Unilateral; discrete	Right	Excision of breast	Duct and fibrous hyperplasia	Lost 18 yrs. later

Case no.	Age	Race	History	Duration (mos.)	Type	Side	Operation	Microscopic diagnosis	Result
12202	22	W	Tumor	3	Unilateral; diffuse	Left	Excision of breast	Duct and marked fibrous hyperplasia (periductal); duct dilatation	Lost 19 yrs. later
12007	45	W	Tumor	6	Unilateral; diffuse	Right	Excision of breast	Marked duct and fibrous hyperplasia (periductal)	Well 11 yrs. later
11763	33	W	Pain; tumor; gradual growth; (excision of tumor 6 mos. previously)	12	Unilateral; discrete	Right	Excision of breast	Duct and fibrous hyperplasia (stroma)	Lost 19 yrs. later
10223	64	C	Trauma ?; tumor; pain	4½	Unilateral; discrete	Left	Radical amputation of breast; axilla	Duct and fibrous hyperplasia	Lost
9669	63	W	Tumor	12	Unilateral; discrete	Left	Excision of breast	Duct and fibrous hyperplasia	Lost 22 yrs. later
0516	62	W	Trauma; tumor; pain	3	Unilateral; discrete	Left	Excision of breast	Duct hyperplasia with papilloma formation	Lost 22 yrs. later
7052	19	W	Tumor	70	Unilateral; discrete	Right	Excision of breast	Marked fibrous hyperplasia (stroma)	Lost 25 yrs. later
7621, 7526	40	W	Tumor	1	Unilateral; diffuse	Right	Complete excision of breast	Marked duct and fibrous hyperplasia (periductal)	Well 24 yrs. later
	..	..	Tumor	..	Unilateral; localized	......	Amputation of breast	Duct and fibrous hyperplasia (stroma)	Dead 22 yrs. later; paralysis
7418	45	W	Burning sensation; tumor	½	Unilateral; diffuse	Left	Amputation of breast	Marked duct and fibrous hyperplasia (periductal)	Well 1½ yrs. later
7402	62	W	Tumor; pain	12	Unilateral; multiple; discrete	Left	Excision of breast	Duct and fibrous hyperplasia (stroma)	Lost 26 yrs. later
6317	19	W	Tumor; slow growth	48	Unilateral; discrete	......	Excision of tumor	Marked fibrous hyperplasia (stroma) duct dilatation	Lost 26 yrs. later
5160	36	W	Tumor	10 yrs.	Unilateral; discrete	Right	Excision of tumor	Fibrous hyperplasia; papilloma	Lost 12 yrs. later
4767	44	W	Amputation right breast (painful hypertrophy); 2½ yrs. later, pain; tumors	1¾	Unilateral; discrete (multiple)	Left	Amputation of breast (left)	Duct and marked fibrous hyperplasia	Lost 27 yrs. later
3569	42	W	Tumors; pain	3	Unilateral; diffuse	Right	Complete amputation of breast	Duct and fibrous hyperplasia	Well 1 yr. later
3329	..	..	Tumor	3	Unilateral; diffuse	......	Excision of breast	Duct and fibrous hyperplasia (stroma)	Lost
3069	25	W	Tumor	..	Unilateral; discrete	Left	Excision of breast	Duct and fibrous hyperplasia (stroma)	Dead 20 yrs. later
1842	20	W	Tumor; pain	..	Unilateral; diffuse	Right	Excision of breast	Duct and fibrous hyperplasia (stroma)	Lost
630	60	W	Trauma; tumor; pain	1½	Unilateral; multiple; discrete	Right	Radical amputation of breast	Dense fibrous stroma	Lost
571	47	W	Trauma; pain; tumor	¾	Unilateral; diffuse	Left	Excision of tumor	Duct and marked fibrous hyperplasia (periductal)	Well 37 yrs. later
569	36	W	Tumor	10 yrs.	Unilateral; discrete	Right	Excision of tumor	Marked duct dilatation; (papillomatous)	Lost
J.C.B. no. 6670	39	W	Trauma; areolar scar	..	Unilateral; discrete	......	Operation not advised	......	Well 16 yrs. later; no recurrence
Surg. no. 1940	43	W	Tumor; slow growth	36	Unilateral; discrete	Right	Excision of tumor	Marked fibrous hyperplasia	Well 1 yr. 8 mos. after operation
376	21	W	Tumor; pain	12	Bilateral; discrete	Right and left	Excision of tumor (right)	Duct and marked fibrous hyperplasia (stroma)	Lost 8 yrs. later
Autopsy 10078	1½ mos.	W	Tumor	11 days	Bilateral; diffuse	Right and left	......	......	Death (pyloric stenosis)

and that occurring in middle-aged and elderly persons as a chronic hypertrophy.

Heredity has been named as a factor in gynecomastia, but the occurrence is so infrequent that it may be classed as incidental. Hutchinson [82] and others [83] have reported such instances. Hereditary influences, however, bring to mind the possibility of inherent atavistic reversion which should not be overlooked in the final analysis of gynecomastia.

PERSONAL STUDY

Statistics on tumors of the male and female breast recorded in the Surgical Pathological Laboratory of the Johns Hopkins Hospital and University reveal that tumors of the male breast occur in 3.6 per cent of the total.

The present study was made from 130 cases of tumors of the male breast collected in the laboratory, the first case being recorded in 1890. Of the 130 cases, 99, or 76.1 per cent, were benign and 31, or 23.9 per cent, were malignant. Of the 99 benign cases, 88 were hypertrophies.

The results of further statistical study of the hypertrophies is shown in the following tabulation:

Race (white), 88%
Age (average), 31-50 years
Youngest case, 1½ months
Oldest case, 74 years
Duration (average), 14.7 months
Duration (extremes), 11 days; 12 years
Location: left, 47.2%; right, 40%

Location (bilateral), 12.8%
Trauma, 14%
Pain, 30%
Tenderness, 50%
Tumor (discrete), 76%
Tumor (diffuse), 31.5%
Result (benign), 100%

A study of the microscopic sections and a correlation of them with the histories, operations and postoperative observations, favor the inclusion of the so-called fibro-adenomas in the classification of gynecomastia. The following case explains and prompted this decision:

A healthy, beardless boy 17 years of age, noted a symptomless, bilateral, symmetrical enlargement of his breasts. For two years he was ridiculed for having feminine breasts, and on one occasion this deformity prevented his admission into the marine corps. The remainder of the history and physical examination were essentially unimportant. For cosmetic effect, a bilateral amputation of the breasts was performed. The gross specimens (figs. 2A and B) showed a diffuse fibrous hypertrophy. Between the white fibrous strands there were pink semi-translucent and yellow areas. The microscopic picture was typical of so-called fibro-adenoma. There were areas of duct dilatation, which in some places showed early papilloma formation (fig. 3). The close relationship of such fibro-adenomas with the various other phases of hyperplasia found in gynecomastia is brought out in the microscopic description of these lesions subsequently presented.

82. Hutchinson, J.: Gynecomazia, Arch. Surg. **3**:327, 1891.

83. Savitschky: Case of Gynecomastia, St. Louis M. & S. J. **66**:118, 1894. Schaumann, H.: Beitrag zur Kenntnis der Gynäkomastic, Verhandl. d. phys.-med. Gesellsch. zu Würsburg **28**:1, 1894-1895.

HISTOLOGY

The hypertrophy characterizing gynecomastia is infinitely connected with the normal growth of the male breast observed in infancy and at puberty.
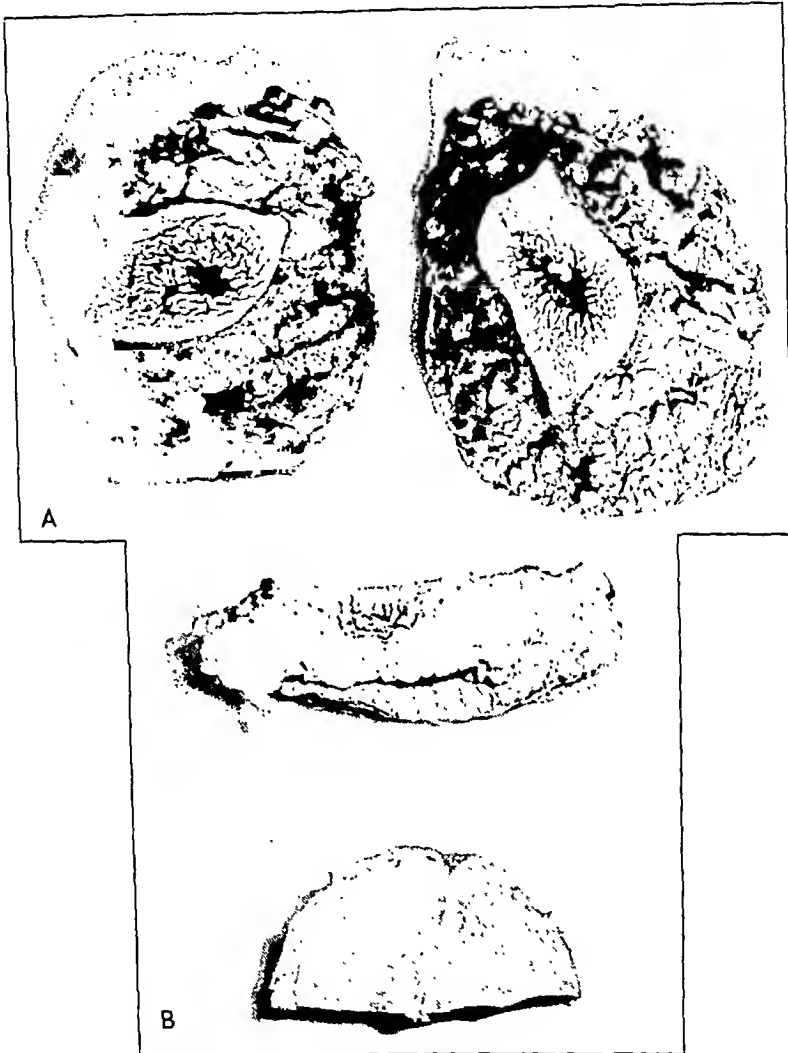
Fig. 2 (path. no. 37042).—*A*, the breasts of a white youth, 17 years of age, which were removed for cosmetic effect because of bilateral symmetrical enlargement. The gross specimens are surrounded by pads of fat with no evidence of glandular tissue (*B*). *B*, cross-section of the breasts showing diffuse, bilateral fibrous hypertrophy which includes pink areas between its strands and a few yellow opacities.

The normal male gland has a tendency to hypertrophy in the first year of life, but after this period development progresses slowly until puberty is reached. At puberty development is at its height. The

parenchyma begins its development as long tubelike processes, descending from the overlying epidermis (fig. 8). The ends of these processes become distended but have no tendency to form lobules. The surrounding stroma is composed of moderately dense fibrous tissue. At the end of the first year of life, and especially at puberty, the parenchyma has a tendency to become hypertrophied and hyperplastic. This hyper-

Fig. 3 (path. no. 37042).—Microscopic section of breast tissue in figure 2, demonstrating an epithelial hyperplasia with beginning papillary formation and desquamation into the duct lumen. The periductal fibrous stroma is dense, collagenous and adult in structure.

plasia is accompanied by the development of two or more rows of nuclei which may be either oval or cylindric in shape. The surrounding stroma forms a variable amount of young and loose periductal connective tissue which contains numerous blood vessels. This hypertrophy is not marked in the majority of cases, and as a rule there is no clinical evidence of its presence.

In gynecomastia the extent of the cell proliferation is dependent on the intensity and the duration of the stimulating influence. When gynecomastia is present, the parenchyma and stroma show evidence of hyperplasia which seems to be more pronounced in cases of short duration.

There is an increase in the epithelial lining of the ducts. The ducts are lined with cells containing a central, small, clear nucleus. As the lumen is approached from the periphery, the cells vary from a cuboidal to a cylindric form, the cylindric form predominating when proliferation is most marked. The lumen is often filled with the eosin-staining
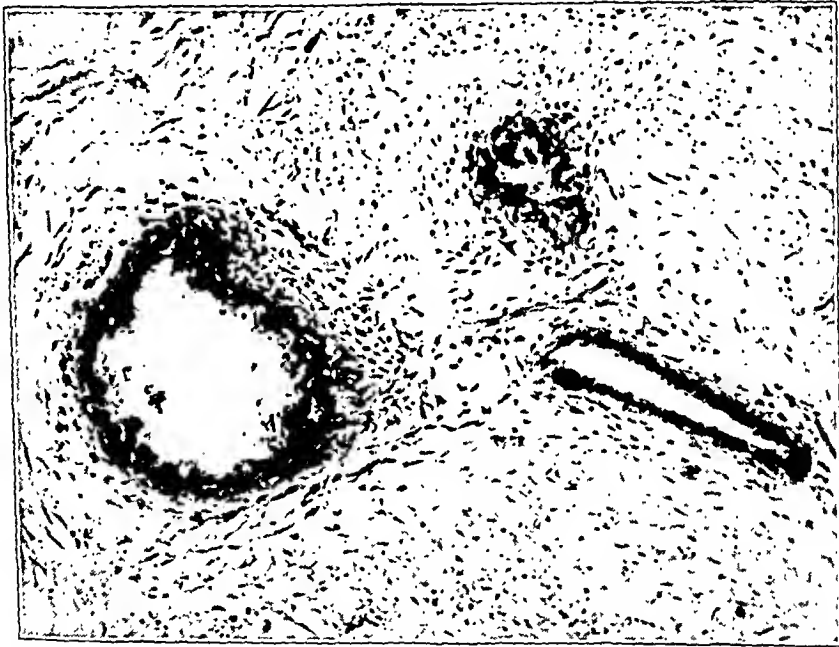
Fig. 4 (path. no. 40630).—Microscopic structure of breast tissues from a white man, 62 years of age, who, for two and one half months, complained of stitch-like pains in his breast. This was associated with a small nodule which produced a retraction of his right nipple. The breast was excised, and the patient is living and well three years later. The microscopic section shows epithelial hyperplasia surrounded by the typical, young, loose, periductal, fibrous stroma seen in early cases of gynecomastia.

material of desquamated cells. The periductal stroma is marked by a proliferation of loose connective tissue containing many young fibroblasts and blood vessels (fig. 4). The active growth which is present in this periductal stroma is sometimes indicated by the presence of mitosis (fig. 5). Immediately surrounding the duct there is a lymphocytic infiltration which is accompanied by plasma cells and a few eosinophils.

If the hyperplasia is present for six or more months the proliferation of the parenchyma is not as marked, but the lumen of the duct contains a greater number of desquamated cells. The lining cells vary from an oval to a cuboidal shape (fig. 6). The stroma also changes its appearance, being characterized by a marked condensation of the periductal connective tissue and a decrease in the number of blood vessels.
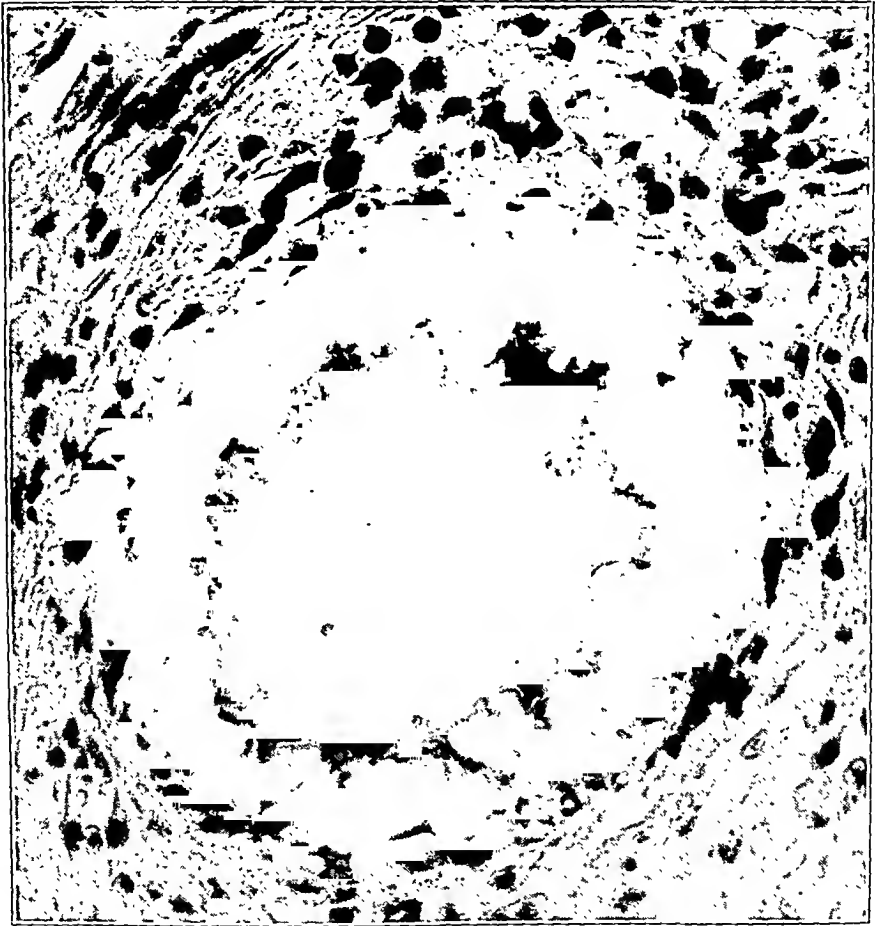
Fig. 5 (path. no. 38464).—Microscopic structure of breast tissue from a white man, 33 years of age, who, for ten weeks, complained of pain and a gradually increasing swelling of his right breast. The tumor was excised, and the patient is living four years later. The microscopic section shows epithelial hyperplasia embedded in a young, fibrous periductal stroma whose rapid growth is indicated by a mitotic figure located immediately above the epithelial lining of the duct.

The hyperplasia of the duct in some cases may take the form of papillomatous proliferation and in later stages may develop into intracystic papillomas (fig. 7). A dilatation of the ducts is frequently seen, but since such dilatations occur in the normal male breast (fig. 8) it is of no great significance.

If a hyperplasia has been present for more than a year, the young periductal connective tissue becomes adult in structure and acquires varying amounts of collagen. A case illustrating such a change is given:

A colored man, 33 years of age, gave a history of having noted a small, tender nodule in his left breast three years previously. After being quiescent for approximately two and a half years, the nodule suddenly became painful and increased in size, two weeks previous to examination.
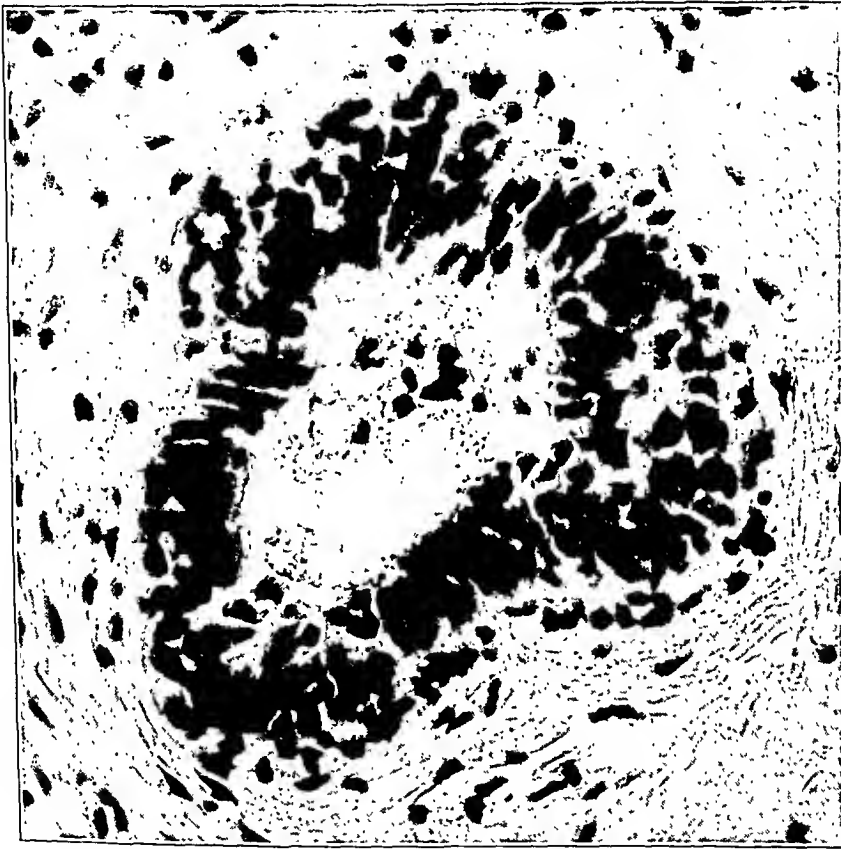
Fig. 6 (path. no. 36144).—Microscopic structure of breast tissue from a colored man, 27 years of age, who, for nine months, complained of a gradual enlargement of his breast associated with sharp, radiating pains. The mass was excised, and the patient is living seven years later. The microscopic section shows an epithelial hyperplasia, with the cells varying from oval to cuboidal in shape. Many of these cells have desquamated into the duct lumen. The periductal stroma is composed of adult fibrous tissue.

Physical examination gave essentially unimportant results except for a flat, firm, slightly tender, freely movable, lobulated tumor, underlying the nipple and located in the upper and outer quadrant of the left breast. After a diagnosis of a benign lesion, a biopsy was decided on.
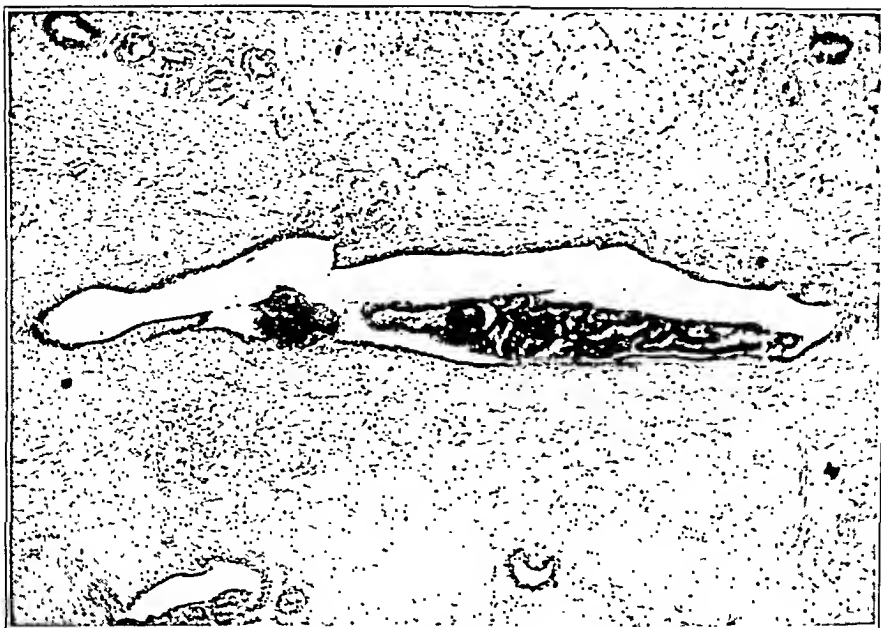
Fig. 7 (path. no. 23500).—Microscopic structure of breast tissue from a col-
ored man, 33 years of age, who complained of a slowly growing nodular mass in
his left breast which was painful at times. The duration was three years. The
mass was excised, and the patient had an uneventful recovery. The microscopic
section shows a typical intracystic papilloma in a case of gynecomastia. Since
different stages of papilloma formation have been noted in gynecomastia (fig. 3),
papilloma may be considered one of the later stages of that condition.

Fig. 8 (path. no. 12265).—Microscopic structure of breast tissue from the
nipple of the normal breast of a white man, 35 years of age, showing a dilatation
of the mammary duct.

The mass was excised and a frozen section proved it to be a benign lesion.

Microscopic examination showed hyperplasia of the duct epithelium with a slight desquamation into the lumen (fig. 9). The periductal stroma was composed of dense, adult fibrous tissue with no evidence of recent hyperplasia. There was no marked periductal infiltration of wandering cells.

The patient made an uneventful recovery, but the ultimate result is not known for all trace of the patient is lost thirteen years later.

The comparison of the foregoing case with the microscopic section (fig. 10) of a 21 year old woman who suffered from a slightly painful

Fig. 9 (path. no. 23500).—Microscopic structure of breast tissue from a colored man, 33 years of age (fig. 8). The microscopic section shows epithelial hyperplasia with desquamation into the duct lumens. The periductal fibrous tissue is dense, collagenous and indicates hypertrophy of long duration.

nodule in her breast for one year shows the close relationship existing between an apparent hypertrophy of a male breast and fibro-adenoma of a female breast.

These studies seem to indicate that hyperplasia grades directly into fibro-adenoma with no definite line of demarcation. Because of this imperceptible gradation, it is impossible to classify borderline cases definitely, and hence the fibro-adenomatous hypertrophy is classed as a further extension of hyperplasia.

SWEAT GLANDS

The intimate relationship of the mammary glands to sweat glands has been proved by Scheifferdecker.[84]   The microscopic resemblance of the mammary ducts to the tubules of the sweat glands is so close in some cases that it is difficult to distinguish between them.   For practical purposes, the chief differentiating point is the presence or absence of desquamation.

The breast, being a holocrine gland, contains desquamating cells in the lumen of its ducts, while the sweat gland, being a merocrene gland,

Fig. 10 (path. no. 2250).—Microscopic structure of the breast tissue from a white woman, 21 years of age, who, for one year, complained of a small painful nodule in her breast.   The mass was excised, and the patient is well five years later.   The microscopic section reveals an epithelial hyperplasia with desquamation into the duct lumen, embedded in a dense adult fibrous stroma.   Compare this fibro-adenoma with the hypertrophy shown in figure 9.

secretes a clear eosin staining material (fig. 11).   The secretion of the large sweat glands, which are located in the breast, are believed by Loeschcke [85] and Scheifferdecker [84] to carry volatile substances which stimulate sex lure.   Von Gusnar,[16] in studying the histology of the male

84. Scheifferdecker: Zoologica, 1922, no. 72.

85. Loeschcke, H.: Ueber zyklische Vorgänge in den Drüsen des Achselhöhlenorgans und ihre Abhängigkeit vom Sexualzyklus des Weibes, Virchows Arch. f. path. Anat. **255**:283, 1925.

breast, demonstrated the different forms of sweat glands resembling the mammae. He also pointed out adenomas of the sweat gland and cystic dilatations occurring in the normal breast which are frequently mistaken for mammary parenchyma.

GROSS DESCRIPTION

Since gynecomastia comprises such a large field, the gross pathology does not present a typical picture. Specimens collected show encapsu-

Fig. 11 (path. no. 44224).—Microscopic structure of sweat glands from a white man, 23 years of age (fig. 12), with gynecomastia. These merocrene glands are frequently mistaken for parenchyma of the breast. They are characterized by a clear, nondesquamated, eosin-staining secretion in their lumens. They are divided into two types, namely, the apokrine (large) and the ekkrine (small) sweat glands. The ekkrine glands are distinguished by their darker staining qualities.

lated, localized or discrete, and diffuse growths. However, in general, the prevailing tissue is fibrous with scattered islands of semitranslucent parenchyma. All the hypertrophies are apparently a variation of this fundamental picture with the supportive element predominating.

The gross specimen (fig. 12 *A* and *B*) usually consists of a uniform, circumscribed mass varying from 2 cm. to 4 inches in diameter. It is usually white, bluish-white or gray and is surrounded by fat, and sometimes by a thin fibrous capsule. It may be attached to the skin, but

Fig. 12 (path. no. 44224).—Specimen from a white man, 23 years of age, with a history of tenderness and a small nodule posterior to the left nipple. Four years after the onset, the mass was excised. The microscopic section confirmed the diagnosis of gynecomastia. The patient is living and well one year later. The gross specimen reveals a circumscribed mass posterior and inferior to the nipple which, on section, shows dense fibrous striations infiltrated with bluish-white tissue and dotted with occasional yellow opacities.

never to the underlying muscles. The consistency may be hard, firm, rubbery or soft.

The mass is easily sectioned, and on detailed examination it usually reveals a homogeneous, white, bluish-white or gray surface which may be dotted with pink or grayish, translucent areas projecting between the strands of fibrous tissue. Yellow opacities may also be found on the cut surfaces.

The acute and diffuse hypertrophies usually have a white or bluish-white translucent appearance, while the chronic and localized forms usually present a white, gray, opaque surface.

DIAGNOSIS

All swellings of the male breast are not produced by hyperplasias. This fact is evident from an examination of the present series of benign tumors of the male breast which includes dermoid cyst, lipoma, lymphangioma and the specific infections of tuberculosis and syphilis, together with nonspecific infections.

From the statistics already given (see tabulation), gynecomastia is more prevalent in the white race; it occurs more frequently in persons between 31 and 40 years of age (fig. 13); it has an average duration of 14.7 months; it occurs equally on the right and left sides; it is bilateral in 12.8 per cent of the cases; it may recur; it is not usually associated with trauma or pain (fig. 14); it is associated with tenderness in 50 per cent of the cases; the tumor is usually single, and is multiple in only 6.2 per cent of the cases. The consistency varies from soft and moderately firm to rubbery and hard.

The recognition of diffuse hypertrophies, both unilateral (fig. 15) and bilateral, is comparatively easy. However, the presence of a discrete nodule presents a more complex picture (fig. 16). A history of fluctuation in size, a multiplicity of lesions and a bilateral occurrence are in favor of a benign lesion.

In spite of the fact that malignancy is evident neither in the microscopic picture nor in our follow-up reports, such a development may occur. Berns [85] reported that a cancer developed in one of two enlarged mammary glands of a man, and that it was the ultimate cause of death. He stated that the breasts were similar to those of a woman and that the carcinoma recurred after an amputation. Among his case reports on gynecomastia, Erdheim [57] included a malignant intraduct papilloma. Twenty-three per cent of the tumors of the male breast are malignant; therefore, whenever a nodule is palpated, malignancy should be definitely ruled out or confirmed. If the mass shows no tendency to fluctuate in size, if it continues to grow or if it presents an indefinite picture, a biopsy and frozen section of it should be made.
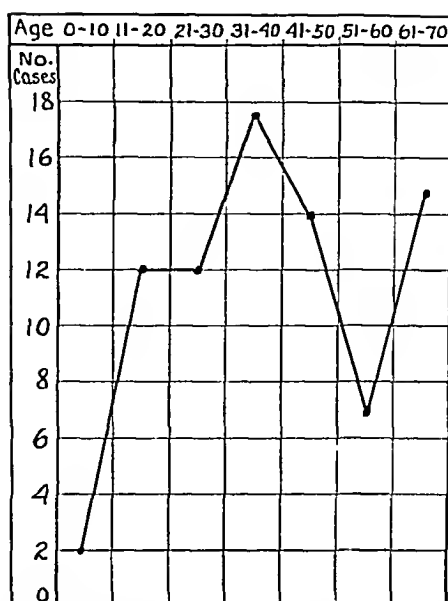
Fig. 13.—Chart of the age incidence in eighty cases of gynecomastia.
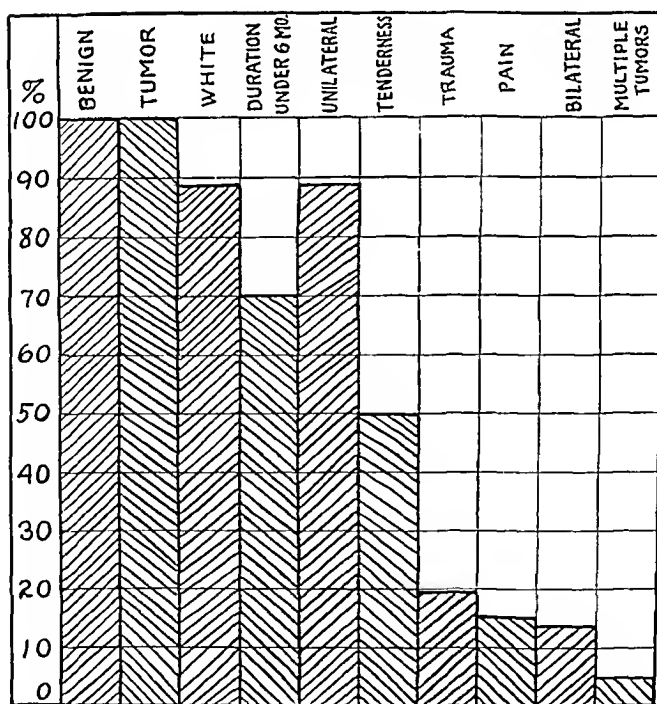
Fig. 14.—Chart indicating the percentages of the outstanding signs and symptoms in the present series of eighty-eight cases of gynecomastia.

TREATMENT

In view of the findings on roentgen treatment recently reported,[86] it should be given a trial in all cases of acute hypertrophy. Evidence leads to the belief that chronic hypertrophies are unaffected by irradiation therapy.

Diffuse enlargements without nodular formation which do not respond to irradiation should be let alone unless the patient insists

Fig. 15 (path. no. 32768).—Diffuse symmetrical enlargement of the right breast in a white boy, 12 years of age. There was a history of gradual, diffuse, painful swelling of six months' duration. Three deep roentgen treatments were administered with a gradual and, finally, a complete disappearance of the tumefaction four months after the last treatment. The patient is living and well, with no recurrence eight and a half years after the last treatment.

on removal for cosmetic purposes. In such cases, plastic surgery may be resorted to. As a rule, the nipple is of little consequence to the male patient and in such cases an elliptic excision, including the nipple, areola and breast tissue, may be made. However, when the breast is greatly

86. Menville, John G.: X-Ray Treatment in Gynecomastia. Radiology, to be published.
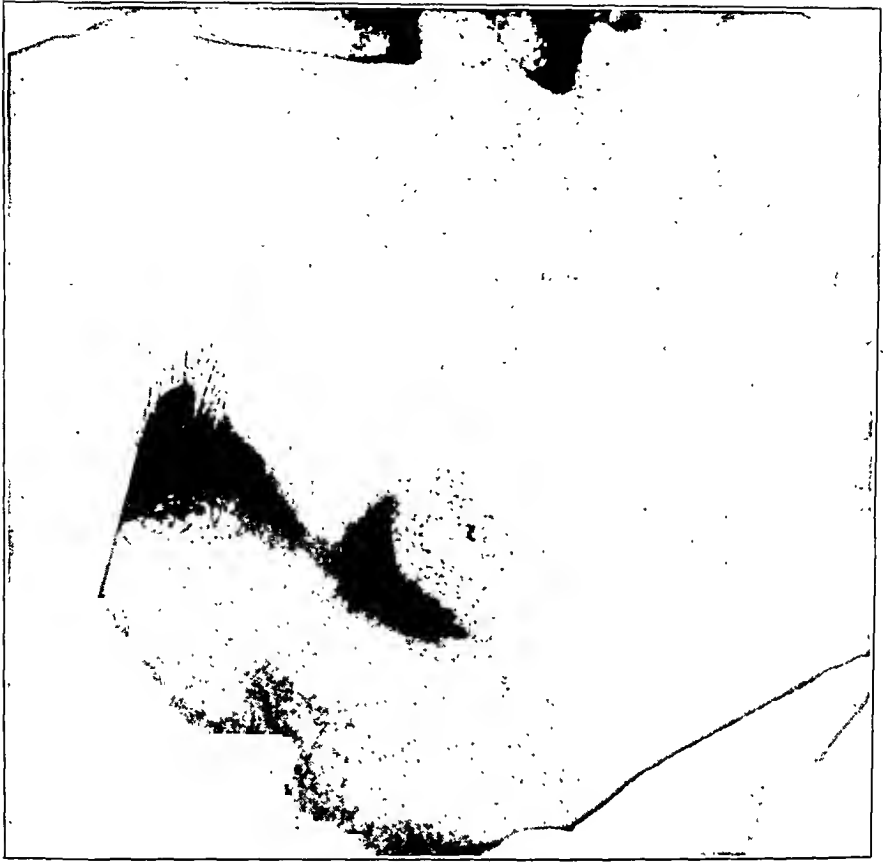
Fig. 16 (path. no. 24617).—Circumscribed discrete swelling posterior and lateral to the right nipple in a white man, 48 years of age. There was a history of a gradually growing nodular mass posterior to the nipple of three years' duration. The breast was excised, and the patient is well eight years later.

Fig. 17.—View of a whole male breast section showing the appearance of gynecomastia at very low magnification. This breast was removed because malignancy was feared. High power magnification verified the diagnosis of gynecomastia.

enlarged and the patient does not care to lose the nipple, the operator may utilize a thoracolateral incision at the junction of the edge of the breast and thoracic wall. This latter incision saves the nipple, leaves a minimal scar and permits the removal of breast tissue. Pain, which may be associated with diffuse hypertrophies, may be treated by suggestion, although if it proves to be a constant source of physical and mental anxiety excision should be performed.

A good rule to follow in hypertrophies which are either composed of, or include, a discrete nodule is to do a biopsy and make a frozen section in order to rule out malignancy. The biopsy performed in cases of localized hypertrophy should constitute a total excision of the tumor mass. Such a procedure answers the purposes of both diagnosis and treatment.

PROGNOSIS

The present series reveals no evidence of malignant change in 88 cases of gynecomastia. However, the isolated reports in the literature of such cases serve as a warning that this possibility should always be remembered. The prognosis concerning the deformity is good if the proper treatment is instituted.

CONCLUSIONS

1. Gynecomastia results from general and local factors.

2. A study of 130 cases of tumors of the male breast revealed:

(*a*) The hypertrophies occurred in 88.8 per cent of the total cases.

(*b*) The so-called fibro-adenoma is a further development of hypertrophy of the male breast (gynecomastia).

(*c*) Fibro-adenoma is included in the classification of gynecomastia.

3. All doubtful cases presenting a discrete nodule should have the benefit of a biopsy and a frozen section to rule out malignancy.

DUODENAL ILEUS

EFFECT OF CHRONIC DUODENAL OBSTRUCTION ON EVACUATION OF THE GALLBLADDER

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One of the phases of chronic duodenal ileus which has attracted particular attention is the relation between it and the function of the biliary tract. Every clinical description of duodenal ileus includes, as one of its frequent manifestations, a symptom complex which simulates disease of the gallbladder.[1] Epigastric distress coming on shortly after meals, pain in the right hypochondrium with scapular radiation, eructation and even jaundice have been described either with or without organic changes in the biliary tract.[2] Orndoff [3] suggested a relationship between the disturbances of duodenal motility so frequently seen in pregnancy and the cholecystic symptoms and disease which may attend and follow it. Duodenal ileus is said in some way to render the biliary tract more liable to infection.[4] Wheelon [5] found an involvement of the biliary structures in 75 per cent of seventy-four patients with duodenal ileus. A cholecystitis had developed in thirty-three cases, hepatitis in fourteen and peribiliary adhesions in forty-eight. In the remaining cases the biliary structures were unchanged.

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2. Higgins, C. C.: Chronic Duodenal Ileus: With a Report of Fifty-Six Cases, Arch. Surg. **13**:1 (July) 1926.

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4. Bockus, H. L.: Intermittent Arteriomesenteric Occlusion of the Duodenum with Dilatation and Stasis, Pennsylvania M. J. **32**:618, 1929. Terris, E.: Les sténoses fonctionelles du duodénum, Rev. de méd., Paris **43**:163, 1926.

5. Wheelon, Homer: Symptoms Associated with Duodenal Retention and Reverse Motility, J. A. M. A. **86**:326 (Jan. 30) 1926

Physiologic interest has centered on the much disputed rôle of the duodenum in the control of biliary outflow. One or more, or all, of the factors proposed, such as contraction of the musculature of the gallbladder, elastic recoil of the wall of the gallbladder, biliary secretory pressure with suction action on the gallbladder contents by the common bile duct stream flowing past the cystic duct and the changes in the intra-abdominal pressure with respiratory movements, empty the glallbladder and carry bile to the duodenum.[6] Because of the long and oblique insertion of the common bile duct in the substance of the duodenal musculature, the waves of duodenal peristalsis sweeping downward are said to exert an important milking action on biliary flow.[7] Aspiration, by the reduced pressure in the duodenum which follows each peristaltic wave, serves to complete the discharge of bile.[8] Resistance to the outflow of bile is controlled by tonus changes in the duodenal wall,[9] by a special sphincter at the orifice of the duct,[10] or perhaps by both.[11]

In the following experiments, the attempt was made to reproduce artificially the conditions of duodenal ileus, to alter duodenal tonus and motility and to study the changes which this might produce in the evacuation mechanism of the gallbladder.

METHOD

In the course of certain studies on the etiology of gallstones, Walsh and Ivy,[12] in an attempt to obtain stasis of bile through a permanent alteration in duodenal motility, employed a method of duodenal reversal. A 2 inch (5 cm.) segment of

6. Ivy, A. C.: Newer Physiology of the Gall-Bladder, Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North America 5:378, 1930. Mann, F. C.: The Functions of the Gall Bladder, Physiol. Rev. 4:251, 1924. Higgins, G. M., and Mann, F. C.: Observations on the Emptying of the Gall Bladder, Am. J. Physiol. 78:339, 1926.

7. Carlson, A. J.: Physiology of the Liver: Present Status of Our Knowledge, J. A. M. A. 85:1468 (Nov. 7) 1925. Copher, G. H.; Kodama, S., and Graham, E. A.: The Filling and Emptying of the Gall Bladder, J. Exper. Med. 44:65, 1926.

8. Burget, G. E.: The Regulation of the Flow of Bile, Am. J. Physiol. 74:583, 1925.

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10. Elman, R., and McMaster, P. D.: Physiological Variations in Resistance to Bile Flow to Intestine, J. Exper. Med. 44:151, 1926.

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12. Walsh, E. L., and Ivy, A. C.: Observations on the Etiology of Gall Stones, Ann. Int. Med. 4:134, 1930.

the third portion of the duodenum was excised from duodenal continuity without disturbing its mesentery or blood supply. It was then turned 180 degrees on its transverse axis and sutured at both ends to reestablish duodenal continuity. Its distal end, however, was then directed orally; its proximal end, aborally. The normal peristaltic activity of the reversed segment would thus be directed up-stream, opposed to the peristaltic drive from above, producing in effect a physiologic duodenal obstruction. In the course of eight months, this led to certain morphologic and chemical evidences of biliary stasis in Walsh and Ivy's cases. There was a marked hyperplasia of the mucosa and lymphoid tissue of the gallbladder. At autopsy the bile was found to be thick, and it contained sediment of the pigment and carbonate type. To reproduce duodenal ileus we employed, at first, this reversal method.

Rather small dogs (from 8 to 12 Kg.) were used generally to facilitate handling under the x-ray machine and fluoroscope. Control studies of the gastric and duodenal activity were conducted, and control emptying times of the gallbladder and stomach were determined before operation. The method of combined visualization, suggested by Levene and Whitaker,[13] clinically, was found to be useful and reliable in the dog. In general, for visualization of the gallbladder, the technic described by Boyden,[14] Graham [15] and Copher [16] was used. No food was allowed on the day of the injection of the dye. Tetiothalein sodium (Mallinckrodt) in a single dose of 0.15 Gm. per kilogram of body weight, dissolved in 30 cc. of water with 2 drops of 2 per cent sodium hydroxide and filtered through China silk, was sterilized in the autoclave. It was injected intravenously at 5 p. m. Thereafter, water also was withheld. At 8 a. m. the next morning, fifteen hours later, roentgenograms were taken. When good visualization of the gallbladder was determined, a combined motor and gallbladder emptying meal was given. The meal consisted of 120 cc. of 20 per cent cream, two egg yolks, 16 Gm. of barium sulphate and enough water to make a total bulk of 240 cc. Fluoroscopy was conducted, and roentgenograms were taken at sufficiently frequent intervals to determine the time required for emptying of the gallbladder and for emptying of the stomach, and to make observations on duodenal motility. This simultaneous study of gastroduodenal and gallbladder activity admits of closer correlation of the results obtained, but the readings made on separate study of each activity were just about the same.

Generally, under the conditions described, the gallbladder emptied in from one and one-half to two hours. In one dog it took three hours, and in two others it

13. Levene, G., and Whitaker, L. R.: New Methods for Clinical Study of Gall-Bladder: Elaboration of Cholecystography with Simultaneous Examination of Stomach and Duodenum, New England J. Med. **202**:203, 1930.

14. Boyden, E. A., and Birch, C. L.: Reaction of the Gall Bladder to Stimulation of the Gastro-Intestinal Tract: Response to Substances Injected into Duodenum, Am. J. Physiol. **92**:287, 1930. Boyden, E. A.: Effect of Natural Foods on Distention of the Gall Bladder, Anat. Rec. **30**:333, 1925.

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16. Copher, G. H.: Cholecystography: Appearance and Disappearance of the Shadow, J. A. M. A. **84**:1563 (May 23) 1925.

took five hours. No reason could be found for these normal departures from the average, and repetition of the experiments confirmed within from one-half to one hour the normal control emptying time of these dogs. The stomach emptied itself in from four to five hours. In only one dog did it take six hours. The range of normal gastric evacuation time was found to be somewhat greater than that of the gallbladder, viz., from one to two hours. Before operation no duodenal stasis, dilatation or antiperistalsis was ever observed. Duodenal peristalsis was uniform, rhythmic and infrequent.

RESULTS

The effort to produce a chronic duodenal ileus by the reversal method sufficiently marked to give definite fluoroscopic changes was unsuccessful in our hands. Just how long a segment of the small intestine needs to reverse to cause the required amount of physiologic obstruction without killing the animal by too great an obstruction had to be determined by trial and error. At first a 3 cm. segment of the most distal portion of the duodenum was used. At the first determinations taken ten days after operation, the gastric and cholecystic emptying times were exactly the same as before operation. There was no apparent increase in duodenal activity, antiperistalsis, dilatation or stasis. Then a 6 cm. segment of the same portion of duodenum was used, with still no apparent results. Since the reversal of longer duodenal segments would have encroached on the region of the ampulla, it was decided that for longer reversal segments the first loop of jejunum would be used. It was recognized that probably longer segments of jejunum than of duodenum would be required to give the same amount of obstruction. A 15 cm. segment of jejunum was therefore employed. The results were the same—negative. There was what might have been interpreted fluoroscopically as a slight hyperactivity of the duodenum. Autopsy showed a slight hypertrophy of the duodenum, but there were no definite physiologic changes sufficient for the purposes of our experiments.

As a last resort, we reversed a 40 cm. portion of small intestine, beginning proximately quite close to the ligament of Treitz (dog 584). In this small dog the segment represented a considerable portion of the entire small intestine. Ten days after operation, fluoroscopy revealed the duodenum to be fully twice its preoperative diameter. The gastric emptying time was increased by three and one-half hours. The meal remained in the dilated duodenum for fully one hour after the stomach was empty. Peristaltic activity of the duodenum was markedly exaggerated. Wave after wave passed hurriedly down the dilated duodenum in quick succession, with little or no intervals of comparative quiet. The waves would pass down to the reversed segment, stop and charge backward toward the pylorus. Peristalsis and antiperistalsis kept chyme surging rapidly back and forth several times, before a thin stream was

admitted into and beyond the reversed segment. In the reversed jejunal segment activity was increased, but not as markedly as in the duodenum. Chyme was seen to pass in it alternately in both directions, up toward the stomach and down toward the ileum. Beyond the reversed segment chyme passed only distally and quietly. The evacuation time of the gallbladder was markedly increased. Before operation, it had taken only two hours; after operation, the gallbladder required fifteen hours to empty itself completely.

Thirty days after operation there was little change from the picture just described. The evacuation time of the gallbladder was still fifteen hours and the gastric evacuation time was fifteen hours instead of the preoperative four hours. Duodenal hyperactivity, however, was not quite so marked as at the ten day observations, and the dilatation had somewhat subsided. Fifty days after operation everything returned to normal. There was still a slight hyperactivity, but no dilatation, stasis or delay in the emptying of the stomach or gallbladder. Autopsy revealed the reversed segment moderately hypertrophied and the duodenum proximal to it markedly hypertrophied, with no gross changes in the biliary tract or the bile. Whatever the resulting morphologic changes may have been, complete physiologic compensation for the reversal had apparently occurred.

Reversal of a 40 cm. segment of jejunum was tried on a second dog. Even the first observations, taken seventeen days after operation, gave results exactly similar to those before operation. Because of the variability of results and the dog's unexpected facility to compensate even for such large reversals, this method was finally abandoned. It may be that the reversal of still longer segments would finally have given constant and permanent results. However, it mattered little for the purposes of these experiments how the duodenal ileus was produced, and it was decided at this point to change to a more certain method.

Berg and Jobling [17] have described a method of producing chronic duodenal obstruction which gives fairly constant results. An upper right paramedian incision is made; a flap about 4 cm. wide and 4 cm. deep, with its base lateral, is cut in the lateral edge of the posterior sheath. An opening is made in an avascular field of the duodenal mesentery just proximal to the ligament of Treitz. The flap is passed from right to left through this opening and turned back laterally over

17. Berg, B. N.; Meleney, F. L., and Jobling, J. W.: Experimental Chronic Duodenal Obstruction: I. Technic and Physiology, Arch. Surg. **14**:752 (March) 1927. Berg, B. N., and Jobling, J. W.: Experimental Chronic Duodenal Obstruction: Changes in the Blood and Other Pathologic Changes, ibid. **16**:593 (Feb.) 1928.

the duodenum, forming for it a sort of sling or ventral mesentery. The edge of the reflected flap is sutured closely to its own base, by four or five interrupted mattress sutures, in such fashion that a marked constriction of the lumen results. In general, a flap the width of which is one and one-half times the diameter of the duodenum (roughly one-half its circumference) gives, when formed into the sling, an effective degree of constriction without jeopardizing the circulation of the bowel. This is not altogether constant, for both the sling and the wall of the bowel are slightly variably plastic. A few animals were lost because of excessive obstruction or because the sling had ulcerated through, and operations had to be performed a second time on a few animals to take

Fig. 1 (dog 408).—Ten days after operation; two hours after the ingestion of a barium meal. Note the sling constriction in the third portion of the duodenum, with the bulblike dilatation just proximal to it and the moderate dilatation of the rest of the proximal duodenum.

up the slack in the sling and obtain a more effective ileus, but in general the method gave satisfactory results. This method has the advantage over compression by metallic bands in that no foreign body is involved and the sling suspends the duodenum to the ventral abdominal wall so that fluoroscopic visualization is facilitated.

Chronic duodenal obstruction was finally obtained by this method. In eight dogs an ileus was produced which was even more striking than the one positive result described in the reversal method. In all eight dogs, ten days after operation, there were duodenal hyperactivity, anti-

peristalsis, dilatation and stasis. The gastric emptying time was usually, but not always, increased, by from one and one-half to five hours. The contrast between the duodenum proximal to the sling and the jejunum just beyond it was striking (fig. 1). The duodenum in some cases appeared fluoroscopically to be three times its preoperative width. Waves of turbulent peristalsis and antiperistalsis carried chyme quickly back and forth in the duodenum, and only an occasional fine trickle was admitted beyond the obstruction. In comparison with the fluoroscopic findings, the symptoms presented by these dogs were slight. An equivalent degree of duodenal dilatation and hyperactivity in human beings would have been accompanied by attacks of biliary vomiting leading toward tetany and to a marked loss of weight and strength. In these dogs, unless the obstruction soon proved incompatible with life, vomiting occurred only rarely and, if at all, only in the first two postoperative weeks. The animals were kept on the ordinary stock diet, except that bones were prohibited and an extra ration of chopped meat was allowed. They lost weight at first, but after a time regained most of it. There was no anorexia or asthenia despite the widely dilated and hyperactive duodenum.

Duodenal ileus resulted in each case, but the degree of change in each manifestation of the ileus, especially in their relation to one another, varied greatly. Berg and Jobling found the same lack of correlation. Sometimes there was marked hyperactivity with slight dilatation, sometimes slight hyperactivity with a widely dilated duodenum and all variations between. The same variability in relation was noted between duodenal hyperactivity and duodenal stasis, between the dilatation and stasis and between any or all of these conditions with gastric stasis. In two dogs (nos. 408 and 645) no gastric stasis resulted despite the marked duodenal obstruction.

The ileus obtained was permanent in all but one dog. The observations taken thirty and sixty days after operation, and even later, showed essentially the same ileus observed at ten days. There was again, however, a lack of correlation between its individual signs. There was, furthermore, a great variability with each manifestation between its intensity at any one time and that at previous or later readings. Yet the obstruction, in one or more of its variable features, persisted. At subsequent autopsies on these animals, the obstructed duodenums were found to be abruptly wider than the jejunums by from 40 to 80 per cent. The duodenal musculature above the obstruction was hypertrophied to almost twice the thickness of the duodenal muscle below the obstruction. When it is considered that the duodenum was at the same time dilated, the actual hypertrophy is seen to be even greater than the increase in thickness implies. There was no duodenitis, neither was there

evidence of any gross morphologic change in the biliary tract (see also the histologic studies of Berg and Jobling). In only one dog (no. 586) did all manifestations of the ileus, including hyperperistalsis, antiperistalsis, dilatation and stasis, subside. In this animal only a slight obstruction was found at autopsy. The sling admitted fully the tip of the little finger, although at operation it had been left much tighter. The duo-
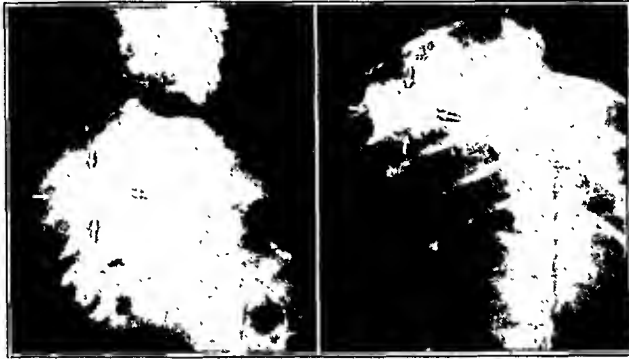
Fig. 2 (dog 598).—Preoperative study of evacuation of the gallbladder. The film on the left shows the gallbladder visualization before the ingestion of a cream-egg yolk meal. The film on the right, taken three hours afterward, shows the gallbladder shadow fainter and smaller. At four and one-half hours only a faint trace of dye remained. At five and one-half hours the gallbladder shadow was absent.
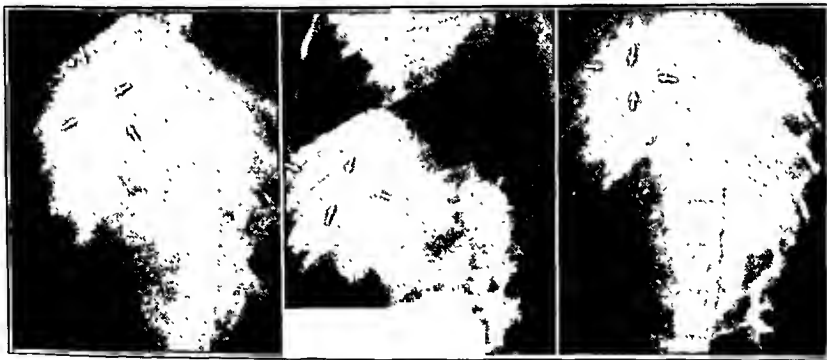
Fig. 3 (dog 598).—One month after operation (sling). The film on the left shows the gallbladder visualization before the ingestion of a cream-egg yolk meal. The film in the middle, taken eight hours afterward, shows the gallbladder of the same size and the same dye intensity. The film on the right, taken fourteen hours later, shows a moderate-sized gallbladder shadow. At eighteen hours only a faint trace of dye remained. At twenty-two hours the gallbladder shadow was absent.

denum above it was also hypertrophied, indicating that at some recent time, at least, a greater obstruction had been present. Stretching of the sling together with a simple increase in the force of peristaltic con-

traction may have been responsible for the gradual subsidence of ileus in this one dog.

In all of the nine dogs in which duodenal ileus had been produced, there was found at first a definite decrease in the efficiency of evacuation of the gallbladder. Ten days after operation, in response to the same emptying meal, the evacuation time of the gallbladder was increased above its preoperative limits. This increase varied anywhere from one to ten hours. Here, too, the degree of increase could not be correlated with all or any one of the manifestations of ileus. Only one conclusion could be derived from these readings; i. e., in all nine dogs the primary result of duodenal ileus was invariably a definite delay in the emptying of the gallbladder (figs. 2, 3 and 4). During the unsuccessful attempts to produce duodenal ileus either by the reversal or by the sling method,

Fig. 4 (dog 584).—One month after operation (reversal). The film on the left shows fasting gallbladder visualization. The film on the right, taken thirteen hours after the ingestion of a combined cream-egg yolk-barium meal, shows a small gallbladder shadow still present, barium in the ileum and colon and a small gastric residue. At sixteen hours the stomach was empty and the gallbladder shadow was absent.

none of the dogs (six) ever showed an increase in the evacuation time of the gallbladder. These dogs served as controls to prove that the ileus and not the operation was responsible for the delay in the emptying of the gallbladder.

In seven of the nine dogs observations on the emptying time of the gallbladder were obtained thirty and sixty days after operation, and even later. In two of these dogs (nos. 342 and 667), in the course of time, the duodenal ileus increased and the delay in evacuation of the gallbladder increased. In two dogs (no. 586, with the sling, and no. 584, with the reversal) all signs of ileus subsided, and with it the evacuation time of the gallbladder returned to normal. In the remaining three dogs

(nos. 598, 619 and 408) the duodenal ileus remained, and yet the emptying time of the gallbladder returned to normal (table).

One incidental experience should be mentioned. Many of the preoperative control animals had to be discarded because of the onset of distemper. It was noted that if the animals were coming down with distemper, even a few days before frank "snuffles" and diarrhea had begun, the biliary flow was sluggish. The evacuation time of the gallbladder in these control animals increased to fifteen, twenty or more hours. We learned to recognize this sign of biliary stasis as a warning

Results

Dog	Condition	Gallbladder, Emptying Time in Hours	Stomach, Emptying Time in Hours	Duodenal		
				Hypermotility	Dilatation	Stasis
442	Before operation	2	4½	0	0	0
	After operation, 10 days	5	7	4+	3+	2+
645	Before operation	1½	4½	0	0	0
	After operation, 10 days	6	4½	4+	4+	2+
342	Before operation	5	5	0	0	0
	After operation, 10 days	6	7	4+	1+	0
	After operation, 30 days	8½	4½	4+	3+	2+
667	Before operation	1½	5	0	0	0
	After operation, 10 days	4	6½	2+	2+	1+
	After operation, 40 days	7	10	3+	4+	4+
586	Before operation	2	4	0	0	0
	After operation, 10 days	9	9	4+	2+	2+
	After operation, 40 days	4	9	2+	2+	2+
	After operation, 60 days	2½	6	1+	1+	0
584	Before operation	2	4½	0	0	0
	After operation, 10 days	15	7½	4+	2+	2+
	After operation, 30 days	15	15	3+	1+	2+
	After operation, 50 days	2	4	1+	0	0
598	Before operation	5	5	0	0	0
	After operation, 10 days	15	9	4+	2+	2+
	After operation, 30 days	20	5	4+	2+	2+
	After operation, 60 days	6	4½	2+	2+	1+
	After operation, 90 days	3½	5½	4+	1+	1+
619	Before operation	3	5	0	0	0
	After operation, 10 days	7	7	4+	2+	2+
	After operation, 30 days	5	3½	4+	0	0
	After operation, 60 days	3½	4	3+	2+	3+
408	Before operation	2	6	0	0	0
	After operation, 10 days	3	6	1+	4+	3+
	After operation, 30 days	6	9	2+	4+	3+
	After operation, 60 days	2½	12	2+	4+	3+

that distemper was beginning, and avoided further use of the animals. Because of the biliary stasis with infection, when distemper developed in any of the animals operated on, further results on them were dropped as unreliable.

COMMENT

According to Alvarez' gradient theory,[18] any given point of intestine is more highly irritable than the next point distal to it, and normal peristalsis, therefore, proceeds only aborally. Antiperistalsis can appear

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18. Alvarez, W. C.: The Mechanics of the Digestive Tract, New York, Paul B. Hoeber, Inc., 1928. Cannon, W. B.: The Mechanical Factors of Digestion, New York, Longmans, Green & Co., 1911.

under conditions of obstruction or local irritation, but otherwise the proximal-distal polarity of the intestine is constant. It is generally believed that this polarity of the peristaltic gradient is irreversible. The surgical reversal of a segment of intestine should therefore direct its peristaltic waves permanently up-stream against the downward drive of the proximal parts of the intestine, and thus produce a definite physiologic obstruction. Yet after each reversal complete compensation occurred, and no permanent ileus was produced.

The failure of the reversal method to produce chronic duodenal ileus may be accounted for by:

1. An exaggerated activity of the intestine proximal to the reversed segment of such force that chyme is propelled through and beyond the reversed segment in spite of the physiologic obstruction which it imposes.

2. An increase in antiperistalsis in the reversed segment proper. This would carry chyme down-stream against the upward drive of normal peristalsis in the anatomically reversed segment.

3. A reversal of physiologic polarity in the anatomically reversed segment. This would direct the peristalsis down-stream again and relieve the obstruction.

That there was no reversal of polarity is suggested by the observation that within the reversed segment chyme was seen to pass alternately in both directions. It was carried distalward either by propulsion by the duodenum proximal to the reversed segment or by antiperistalsis within the reversed segment. It could be carried in the proximal direction, however, only if the normal up-stream directed peristalsis of the reversed segment persisted, i. e., only if polarity was not reversed. This suggestion is supported by the moderate hypertrophy of the muscularis of the reversed segment. If reversal of polarity had occurred, the reversed segment would not be driving chyme up-stream, and hypertrophy would not have taken place. The marked hypertrophy of the proximal duodenum attested further to the persistent resistance to the aboral passage of chyme in the reversed segment, which had to be and was successfully overcome by an increased motor drive of the intestine proximal to it.

The duodenal ileus obtained by the sling method, by reason of its anatomic character, was practically constant. It was also fairly uniform except for slight unavoidable differences in the formation of the sling. It, too, however, elicited all the means of compensation which could be applied. Peristaltic activity and muscular tonus of the duodenum proximal to the sling increased. With a given obstruction, if the tonus increases markedly, there is little dilatation; if only slightly, there is more dilatation.[19] With a given increase of tonus the greater the obstruction the

19. Koennecke, W., and Meyer, H.: Klinisches und Experimentelles zur chronischen Duodenalstenose, Deutsche Ztschr. f. Chir. **175**:179, 1922.

wider will be the dilatation. Stasis results only when the obstruction is greater than peristaltic efficiency can easily overcome.[20] As long as gastric peristaltic efficiency can meet its increased load there is no gastric stasis. If the duodenum can similarly meet its increased load, there is no duodenal stasis. Antiperistalsis appears because of the local exaggerated irritability. But in spite of the counter, up-stream drive, peristalsis and tone can be so elevated that no stasis results. However, peristaltic reaction and tone vary greatly even normally.[21] On the individual differences and variations which arise in them depend the differences in activity, dilatation and stasis which were obtained.

In all cases in which duodenal ileus was produced, the primary result was a definite increase in the evacuation time of the gallbladder. The late results were variable. The possible effects of duodenal ileus on the emptying of the gallbladder are manifold:

1. Chemical irritation of the duodenum will delay the emptying of the gallbladder.[22] In our experiments, the stasis of chyme in the duodenum was never so great as to make likely any chemical irritation.

2. Acute distention of the duodenum will delay the evacuation of the gallbladder. The obstructed duodenums in our experiments were usually considerably dilated, but this was a chronic and not an acute effect. It may have been a factor, however, at least in the early changes noted.

3. Dilatation of the duodenum might also be conceived to flatten out the intramural portion of the common bile duct, or to compress or distort it, and thus account for the biliary stasis. No anatomic evidence to this effect could be found, and there was no increase in the size of the common bile duct to suggest that any constant anatomic obstruction to bile flow had even recently been present.

4. Hyperperistalsis, one of the two chief reactions to duodenal ileus, would tend to increase the efficiency of the emptying of the gallbladder by: (*a*) a greater downward milking action on the intramural portion of the common bile duct and (*b*) a greater aspiration effect by the greater and more frequent changes in duodenal pressure.

Antiperistalsis is followed by the same changes in duodenal pressure, and therefore aids biliary flow by the same aspiration effects. The

20. Kellogg, E. L., and Kellogg, W. A.: Chronic Duodenal Stasis, Radiology **9**:23 (July) 1927.

21. Bloomfield, A. L., and Keefer, C. S.: Clinical Physiology of the Stomach: Simultaneous Quantitative Observations on Gastric Secretory Volume, Acidity and Motility, Arch. Int. Med. **38**:145 (Aug.) 1926. Kasabach, H. H.: Effect of Ingestion of Water and of Dextrose Solution on the Emptying Time of the Normal Stomach, ibid. **48**:1237 (Dec.) 1931.

22. Crain, R. C., and Walsh, E. L.: Effect of Acute Chemical Duodenitis upon the Emptying Time of the Gall Bladder, Surg., Gynec. & Obst. **53**:753, 1931.

peristalsis may be considered as opposing biliary flow, however, by the upward milking action.

5. Hypertonus, the second of the two chief reactions to duodenal ileus, would delay the emptying of the gallbladder by exerting a greater intramuscular tension on the portion of the common bile duct traversing it. Hypertonus and hyperactivity are roughly but not accurately correlated. The increase in peristalsis may be much greater than that in tonus, so far as the effect on biliary flow is concerned. On the other hand, tonus may be so great that peristalsis is stopped. The final effect on the biliary flow would depend on the balance between these factors.

Under the fluoroscope, between duodenal dilatation and hyperactivity, one may obtain a rough estimate of the tonus of the duodenal musculature. However, changes in tonus may well occur independently of these and may not be detectable by this method of observation.

This fact may be sufficient to account for the variability of our late results, but other factors must also be considered. Tonus changes in the sphincter of Oddi may occur independently of tonus changes in the duodenum or of peristalsis and may compensate for them. Perhaps longer contact of food in the duodenum produces more "cholecystokinin" and gives better contraction of the gallbladder. The musculature of the gallbladder, the biliary secretory pressure and the changes in the intra-abdominal pressure may determine their own compensation for whatever obstruction duodenal ileus imposes on the biliary flow.

The inconstancy of our late results is in keeping with the clinical variability of involvement of the gallbladder in duodenal ileus. In some cases biliary stasis results; in others, the duodenal changes or compensating factors are such that biliary stasis does not follow. The delay in the emptying of the gallbladder which was noted with the onset of distemper may have a clinical application. It indicates that the finding of good visualization with poor emptying of the gallbladder may be present even in extracholecystic disease.

CONCLUSIONS

1. The initial result of experimentally produced duodenal ileus in the dog is a definite increase in the evacuation time of the gallbladder.

2. When the operative procedure did not result in duodenal ileus, or if ileus later subsided, the emptying of the gallbladder was as rapid as in the preoperative controls.

3. The late results when ileus persisted were inconstant. In some dogs the delay in the evacuation of the gallbladder persisted; in others, the emptying time of the gallbladder returned to normal. This is in keeping with the clinical variability of biliary involvement in duodenal ileus. Possible explanations for these variations are discussed.

4. The symptoms of duodenal ileus produced in the dog were much less marked than those produced in man by an equivalent degree of anatomic obstruction.

5. The ability of the proximal part of the intestine to compensate for the physiologic obstruction induced by reversal of an intestinal segment in the dog is great. It is probable that this compensation occurs by an increased motor drive of the proximal intestine and perhaps also by increased antiperistalsis in the reversed segment, rather than by any actual reversal of physiologic polarity.

6. The delay in evacuation of the gallbladder noted with the onset of distemper is suggested as of clinical importance in that it is possible to obtain this finding in extracholecystic disease.

PERITONITIS

EFFECTS OF THE ADMINISTRATION OF SALT SOLUTION ON THE AMOUNT OF FLUID THAT ACCUMULATES IN THE PERITONEAL CAVITY

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There has been a growing tendency in recent years to inject large quantities of fluids intravenously in the treatment of shock, peritonitis and intestinal obstruction. MacFee and Baldridge,[1] 1930, reported their results in the treatment of such conditions by the intravenous injection of large amounts of physiologic solution of sodium chloride. They stated that: "The solution has been given intravenously in amounts ranging from 2000 cubic centimeters to 8000 cubic centimeters at a single injection. The usual amount required has been about 4500 cubic centimeters." Autopsy was performed recently on a patient who died of peritonitis and who had been given large amounts of salt solution intravenously. The peritonitis was generalized, and there was an unusually large amount of fluid in the peritoneal cavity. Following this autopsy it was feared that the extent of the peritonitis had been increased by the fluid that had been introduced and that the patient's chances of recovery had been lessened.

The present experiments were performed in order to determine the amount of free fluid that was present in the peritoneal cavities of dogs with peritonitis, to some of which no fluid had been given and in others of which fluid had been introduced intravenously or subcutaneously.

METHODS

All of the experiments were performed on dogs. Two types of slightly different experimental procedures were carried out. In the first group of experiments, the meso-appendix was ligated and divided, and an opening was made that extended half across the appendix at the junction of the proximal and middle thirds. These animals were studied until they died or until it was seen that they were going to recover. If an animal lived for less than twenty-one hours following the operation or if it recovered, the experiment was discarded. In the second group of experiments, an opening was made half across the appendix at the junction of the proximal and middle thirds. The meso-appendix was not divided. Bleeding was controlled by suture ligatures. These animals were killed, and autopsy was performed approximately forty-eight hours following the operation. The experiments in

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1. MacFee, W. F., and Baldridge, R. R.: Postoperative Shock and Shocklike Conditions: Treatment by Infusion in Large Volume, Ann. Surg. **91**:329, 1930.

which the animals survived less than forty-five hours were discarded. Ether was used as the anesthetic for the operations.

The rest of the procedures were common to both types of experiments. In order to keep the animals quiet while fluids were being administered, they were given each day 0.033 Gm. of morphine sulphate prior to the beginning of the injection. In order to maintain conditions as uniform as possible and also because morphine is used in treating peritonitis, the animals not receiving fluids were also given morphine each day. No fluids or food were given by mouth following the operation. As has been stated, physiologic solution of sodium chloride was introduced intravenously in some experiments and subcutaneously in some; the remaining animals received no fluids.

The femoral vein was chosen for the intravenous injections. The subcutaneous injections were made into the tissues of the thigh and flank. The fluid was introduced each day following the operation; it was at body temperature and was given at a constant rate for a period of four hours. Ten cubic centimeters of fluid to a kilogram of body weight was given every hour for four hours.

Following the death of the animal, the body weight was determined. A midline abdominal incision was then made, and a sample of the free fluid was obtained for subsequent study. All of the free fluid was then sponged away from the peritoneal cavity. The animal was weighed again, and the difference in the weight before and after the removal of fluid was determined in grams. This figure gave approximately the number of cubic centimeters of free fluid in the peritoneal cavity.

The nitrogen content of the fluid that was obtained from the peritoneal cavity was determined by the Gunning [2] modification of the Kjeldahl method. In the tables the nitrogen is expressed as protein.

RESULTS

The percentage of deaths that occurred in less than twenty-four hours following the operation was greater in the group in which the meso-appendix was ligated and divided.

Experiments in Which the Meso-Appendix Was Severed and an Opening Made Into the Appendix.—After a few experiments had been performed, it was realized that conclusions as to the relative merits of giving no fluids and of administering salt solution subcutaneously or intravenously in preserving or lengthening the life of animals with peritonitis could not be drawn from the experimental procedures used in this work. It would require a tremendous number of experiments to determine this point. Many animals died within less than twenty hours following the operation, and since fluids were not injected until the day following operation, these experiments are not included in the tables. One or more animals in each of the three groups, namely, those receiving no fluid, those receiving salt solution intravenously and those receiving it subcutaneously, appeared to be in good condition the fourth day following the operation and were given food and water

2. Gunning, J. W.: Ueber eine Modification der Kjeldahl-Methode, Ztschr. f. anal. Chem. **28**:188, 1889.

by mouth. They recovered from the operation and are not included among those reported here.

The largest amount of free peritoneal fluid per kilogram of body weight was found in the experiments in which the salt solution was injected intravenously. The average number of cubic centimeters was 40.9. The average number of cubic centimeters per kilogram of body weight in the experiments in which no solutions were injected was 18.5, and it was 14.7 cc. in those in which the salt solution was given

TABLE 1.—*Showing the Effects of No Fluids, of Fluids Introduced Intravenously and of Fluids Injected Subcutaneously in Dogs in Which the Meso-Appendix Had Been Divided and an Opening Had Been Made into the Appendix*

Method of Adminis- tration of Fluid	Ex- peri- ment	Weight of Dog, Kg.	Time Lived After Operation	Interval Between Last Fluid and Death	Total Fluid Intro- duced, Cc.	Fluid in Peri- toneal Cavity, Cc.	Fluid in Peri- toneal Cavity, Cc. per Kg. Body Weight	Protein, Gm. per 100 Cc.
No fluid	1	14.8	30 hrs.	....	0	325	21.9	5.58
	2	13.5	24 hrs.	....	0	180	13.3	4.33
	3	13.0	45 hrs. 30 min,	....	0	290	22.3	6.49
	4	10.7	48 hrs.	....	0	65	6.1	4.26
	5	15.6	37 hrs.	....	0	480	30.7	6.30
	6	16.0	21 hrs.	....	0	270	16.9	....
Average.....							18.5	5.43
Fluid intra- venously	1	20.5	46 hrs. 30 min.	1 hr. 30 min.	1,640	1,400	68.3	4.59
	2	16.4	46 hrs. 30 min.	1 hr. 30 min.	1,312	500	30.5	3.24
	3	15.4	84 hrs.	12 hrs.	1,848	1,160	75.3	4.75
	4	11.4	28 hrs. 50 min.	3 hrs.	456	300	26.3	5.04
	5	5.8	30 hrs. 50 min.	10 hrs.	230	140	24.1	6.50
	6	9.6	84 hrs.	12 hrs.	1,153	200	20.8	6.81
Average.....							40.9	5.16
Fluid subcuta- neously	1	12.1	45 hrs.	20 hrs.	484	180	14.9	5.83
	2	16.1	30 hrs. 45 min.	7 hrs.	644	160	9.9	5.81
	3	13.5	31 hrs.	8 hrs. 30 min.	540	305	22.6	5.36
	4	8.1	22 hrs.	1 hr.	324	80	9.9	....
	5	9.3	60 hrs.	12 hrs.	744	135	14.5	5.59
	6	11.2	24 hrs.	0 hrs.	400	170	15.2	....
	7	7.9	49 hrs.	1 hr.	633	125	15.8	4.65
Average.....							14.7	5.49

subcutaneously. It is surprising that there was a slightly larger amount of free peritoneal fluid in the experiments in which no fluid was injected than in those in which it was given subcutaneously, and this probably would not have been the case if the number of experiments had been greater. This finding was reversed in the second type of experiments to be reported later in this paper. There was little difference in the average protein content of the peritoneal fluid in the three groups of experiments. The lowest values were found in the experiments in which the fluid was given intravenously.

The results of these experiments are given in table 1.

Experiments in Which an Opening Was Made Into the Appendix.—
The experiments were discarded in which at the expiration of the
forty-eight hour period no free fluid was found in the peritoneal
cavity. Such a finding was the exception rather than the rule. The
largest amount of free fluid was found in the experiments in which
salt solution was injected intravenously. The average number of cubic
centimeters per kilogram of body weight in these experiments was 34.
The corresponding figure in the experiments in which fluid was given

TABLE 2.—*Showing the Effects of No Fluids, of Fluids Introduced Intravenously
and of Fluids Injected Subcutaneously in Dogs in Which an Opening Had
Been Made into the Appendix. Dogs Killed Approximately
Forty-Eight Hours After Operation*

Method of Administration of Fluid	Experiment	Weight of Dog, Kg.	Length of Experiment, Hours	Total Fluid Introduced, Cc.	Fluid in Peritoneal Cavity, Cc.	Fluid in Peritoneal Cavity, Cc. per Kg. Body Weight	Protein, Gm. per 100 Cc.
No fluid	1	14.8	46	0	25	1.7	7.66
	2	18.5	52	0	275	14.9	7.41
	3	19.0	51	0	135	7.1	5.75
	4	11.5	51	0	140	12.2	6.32
	5	10.9	50	0	55	5.0	5.91
Average........................						8.2	6.61
Fluid intravenously	1	10.1	40	808	670	66.3	5.55
	2	11.0	49	880	260	23.6	2.73
	3	12.8	45	1,024	565	44.1	4.63
	4	8.6	45	680	165	19.2	5.06
	5	8.9	51	712	150	16.9	5.23
Average........................						34.0	4.65
Fluid subcutaneously	1	9.5	46	756	115	12.1	5.63
	2	9.3	46	746	170	18.3	5.35
	3	8.5	45	673	170	20.0	5.00
	4	10.5	49	842	35	3.3	4.73
	5	7.0	45	556	75	10.7	5.23
	6	10.3	50	821	130	12.6	4.70
	7	11.5	45	920	100	8.7	5.14
Average........................						12.2	5.11

subcutaneously was 12.2 cc., and in those in which no fluid was given, it
was 8.2 cc. The protein content of the free peritoneal fluid was
highest in the experiments in which no fluid was given, and it was
lowest in the experiments in which salt solution was injected intra-
venously. The results of these experiments are given in table 2.

COMMENT

From these experiments, conclusions cannot be drawn as to whether
the introduction of salt solution intravenously increases or decreases
the chances of recovery of an animal with peritonitis. The fact that
the animals which received salt solution intravenously had on the average

approximately three times as much free fluid as those getting no fluids and those receiving salt solution subcutaneously suggests that the introduction of large amounts of fluids intravenously in the presence of peritonitis may be harmful. If the circulation is in sufficiently good condition to absorb fluids, it is probably better to administer them by some route other than the intravenous one. In the present experiments the introduction of salt solution subcutaneously was associated with approximately the same amount of free peritoneal fluid as the giving of no fluids. The effects of the introduction of fluids by rectal tube were not studied, because usually dogs expel fluid administered by this method.

Beard and Blalock [3] found that the introduction of physiologic solution of sodium chloride intravenously while the intestines were being traumatized was associated with the escape of an unusually large amount of fluid into the peritoneal cavity. The present experiments show that bacterial and mechanical injuries act similarly in this respect.

SUMMARY

The effects on the amount of free peritoneal fluid and on the protein content of this fluid of not giving fluids, of injecting salt solution intravenously and of introducing salt solution subcutaneously have been determined in dogs with peritonitis. No food or water was given by mouth. In the first group of experiments, peritonitis was produced by ligating and dividing the meso-appendix with its vessels and by making an opening into the appendix. These animals were observed until death or recovery took place. In the second group an opening was made into the appendix, and bleeding vessels were ligated. The experiment was terminated approximately forty-eight hours later.

The animals which received salt solution intravenously had an average of approximately three times as much free peritoneal fluid as those getting no fluids and those receiving salt solution subcutaneously. The content in protein of the free peritoneal fluid was lowest in the animals in which salt solution was given intravenously.

3. Beard, J. W., and Blalock, Alfred: Intravenous Injections: A Study of the Composition of the Blood During Continuous Trauma to the Intestines When No Fluid is Injected and When Fluid is Injected Continuously, J. Clin. Investigation **11**:249, 1932; The Effects on the Composition of the Blood of the Subcutaneous Injection of Normal Salt Solution into Normal Dogs and into Dogs Subjected to Intestinal Trauma, Graded Hemorrhages and Histamine Injection, ibid. **11**:311, 1932.

EXPERIMENTAL PERITONITIS

THE RÔLE OF THE WELCH BACILLUS

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Probably the most serious types of peritonitis are those in which not only virulent micro-organisms are present in the peritoneal cavity, but, in addition, culture material for the micro-organisms to develop on. This set of conditions is seen in various types of perforative peritonitis or in lesions accompanied by the death of tissue, such as postoperative peritonitis or peritonitis with strangulated hernia. Since it is difficult to produce peritonitis experimentally by the introduction of bacteria alone into the normal peritoneum, it seemed logical to assume that experimental peritonitis could be produced by the introduction of bacteria growing on a culture medium. By such a method it would be possible, theoretically, to study peritonitis produced by a single type of micro-organism or by selected groups of micro-organisms. Accordingly, pure cultures of Bacillus coli, staphylococcus, streptococcus and pneumococcus on agar or blood agar slants were introduced into the peritoneal cavity of dogs and rabbits. Many of these animals became extremely sick, and most of them died or were killed within twenty-four hours. At autopsy, in addition to the original micro-organism introduced into the peritoneal cavity, B. welchii was found to be present, and often predominated in numbers. In some instances, streptococci or staphylococci were found to be present when the original organism introduced was B. coli. The peritoneum was reddened and contained a small amount of serosanguineous fluid with a little fibrin. Blood cultures were not taken in all experiments, but when cultured, they were negative. Control experiments in which plain agar was introduced into the peritoneum gave negative results. A summary of these experiments follows.

EXPERIMENTATION

Medium-sized dogs were selected, and under careful aseptic technic agar slants with a twenty-four hour growth of colon bacillus, streptococcus, staphylococcus or pneumococcus were placed within the peritoneal cavity through a small, lower rectus incision. Seventeen

of the 23 dogs died within from twelve to thirty-six hours of an extensive hemorrhagic peritonitis. The results of this series are given in table 1.

Postmortem examination was made immediately or a few hours after death. Several of the dogs were markedly distended, and gas escaped from the peritoneal cavity when the abdomen was opened. Smears and aerobic and anaerobic cultures were made from the peritoneal fluid. A gram-positive anaerobic bacillus, which was identified as the Welch bacillus, was cultured along with the bacterium that had been growing on the agar slant. Other bacteria were cultured from 6 of the 17 dogs with peritonitis.

TABLE 1.—*Agar Slant and Bacteria Given Intraperitoneally* *

Bacteria	Dogs	Deaths	B. Welchii	Other Bacteria
Colon bacillus..............................	12	9	8	Streptococcus, 1
Streptococcus..............................	5	3	3	Staphylococcus, 1
Staphylococcus..........................	3	2	2	Streptococcus, 2
Pneumococcus..............................	3	3	3	Streptococcus, 2
	Rabbits			
Colon bacillus..............................	4	2	2	None
Streptococcus..............................	2	1	1	None
Staphylococcus..........................	2	1	1	None

Sterile Agar Slant Intraperitoneally

Dogs	Deaths	Postmortem	Cultures
6	0	Negative	Sterile

Physiologic Solution of Sodium Chloride and Colon Bacillus Intraperitoneally

Dogs	Deaths	Postmortem	Cultures
2	0	Negative	Sterile

* The same strain of B. coli was used on an agar slant for introduction into the peritoneum of 2 dogs; death occurred within twenty-four hours of peritonitis from which the Welch bacillus was cultured.

Four dogs were killed after sixteen hours to rule out the possibility of postmorten invasion of the Welch bacillus.

In 6 dogs sterile agar slants were placed intraperitoneally. Postmortem examination of these dogs showed the agar encapsulated, and the cultures were sterile.

The same strain of B. coli that produced a hemorrhagic peritonitis with the invasion of the Welch bacillus was injected intraperitoneally in a physiologic solution of sodium chloride into 2 dogs. Both dogs survived but were killed forty-eight hours later; the peritoneal fluid was sterile.

To rule out the possibility that these experiments were peculiar to dogs, agar slants with B. coli, streptococcus or staphylococcus were placed in the peritoneal cavity of eight rabbits. Four of the rabbits died of peritonitis; Welch bacillus and the bacterium from the agar slant were cultured.

The suspicion arose that the secondary invaders into the peritoneum might come from the nearby intestine by continuity due to damage or inflammation of the wall of the bowel. Accordingly, under aseptic technic a piece of muscle was removed from the abdominal wall or from the hind leg of a dog. In the defect was placed an agar slant with a twenty-four hour culture of the colon bacillus, streptococcus, staphylococcus or pneumococcus. Agar slants with bacteria were also placed between muscle bundles without removal of any of the muscle. Thirteen dogs were used in this group; two deaths occurred. Cultures from the pus of all the wounds showed the Welch bacillus along with the bacterium from the agar slants. Blood cultures were sterile. Gas was palpated in all the wounds. The muscle removed was passed through a Rosenau grinder, and the cultures were found to be sterile.

TABLE 2.—*Agar Slant with Colon Bacillus in the Abdominal Wall**

Dogs	Deaths	B. Welchii
3..	0	2

Sterile Agar Slant in Abdominal Wall		
Dogs	Deaths	Cultures
3..	0	Sterile

Agar Slant with Bacteria in Muscle of Leg			
Bacteria	Dogs	Deaths	B. Welchii
Colon bacillus..	4	1	4
Staphylococcus..	2	1	2
Streptococcus..	2	0	2
Pneumococcus..	2	0	2

* A sterile agar slant was placed in the other hind leg of all the dogs; it always remained sterile.

At the time when the agar slant with a bacterial growth was placed intramuscularly in the hind leg of a dog, a sterile agar slant was placed in a corresponding position in the opposite leg. Also, in 3 dogs sterile agar slants were placed between the muscles of the abdominal wall. The dogs were killed forty-eight hours later, and the cultures were sterile.

These experiments are summarized in table 2.

In order to determine whether local infection was the essential factor in creating conditions favoring the appearance of secondary invading micro-organisms, several types of nonbacterial inflammatory reactions were set up in the peritoneal cavity.

A 50 per cent solution of dextrose, a 5 per cent solution of turpentine emulsion and a 0.3 per cent solution of hydrochloric acid were injected intraperitoneally, and the dogs were killed at the end of twenty-four hours. Postmortem examination showed a slightly inflamed peritoneum with a transudate, but aerobic and anaerobic cultures were

sterile. The possibility of producing peritonitis by chemical irritation of the peritoneum in the presence of mediums for bacterial growth was tried. Sterile agar slants were placed in the abdominal cavity under careful surgical technic along with dextrose or the turpentine solution. The dogs were killed twenty-four hours later, and the cultures were sterile.

Steinberg and Goldblatt[1] reported that they were able to produce fatal peritonitis by the intraperitoneal injection of 40 cc. of a 2.5 per cent solution of tragacanth with B. coli. We repeated their work using the colon bacillus, streptococcus and staphylococcus in 9 dogs; 6 deaths occurred from hemorrhagic peritonitis. Cultures of the peritoneal fluid contained the Welch bacillus along with the bacterium injected. Sterile

TABLE 3.—*Peritoneal Irritation*

1. Dextrose: 50 cc. of a 50 per cent solution: 2 dogs
2. Dextrose: 50 cc. of a 50 per cent solution with 10 cc. of 2.5 per cent solution of iodine: 2 dogs
3. Dextrose and a sterile agar slant: 1 dog
4. Turpentine and a sterile agar slant: 2 dogs
5. 0.3 solution of hydrochloric acid at two hour intervals: 3 dogs

   All dogs survived. Postmortem examinations were negative except for a transudate and adhesions.

40 Cc. of a 2.5 Per Cent Solution of Tragacanth with Bacteria Administered Intraperitoneally

Bacteria	Dogs	Deaths	B. Welchii
Colon bacillus	4	4	4
Streptococcus	2	1	1
Staphylococcus	3	1	1

40 Cc. of a 2.5 Per Cent Solution of Tragacanth Administered Intraperitoneally

Dogs	Deaths	Postmortem	Cultures
3	0	Negative	Sterile

tragacanth injected into 3 dogs had no effect, and the cultures of the peritoneal fluid were sterile.

The results of these experiments, summarized in table 3, show that chemical inflammation of the peritoneum is not followed by the appearance of bacteria in the inflamed area.

Therefore, it can be assumed from these experiments that the secondary invading micro-organisms were not introduced into the tissue from without and were not part of an accompanying blood stream infection; that they did not come directly by extension from the intestinal tract into the peritoneal cavity, and that they therefore must have been present in the tissue at the beginning of the experiment. It seems fair to assume, then, that B. welchii and occasionally other micro-organisms must be seeded into the different tissues of the body in laboratory animals through the blood stream without causing local

1. Steinberg, B., and Goldblatt, H.: Studies on Peritonitis, Arch. Int. Med. **39**:446 (March) 1927.

manifestations until the local resistance of the tissue is lowered by infection, when B. welchii rapidly overgrows the original infection, often with a fatal result.

How do these experimental facts square themselves with clinical and experimental knowledge of this subject, especially as related to anaerobic bacteria?

The Presence of B. Welchii in Human Feces.—As the intestinal tract is the most usual site for B. welchii, it is worth noting that Dudgeon [2] found that in 200 specimens of human feces, B. welchii was present in 35 per cent. Dudgeon also stated that in acute intestinal obstruction and in vomiting accompanying advanced peritonitis, the vomitus contained B. welchii in most instances.

The Presence of Micro-Organisms in the Organs and Blood of Freshly Killed Animals.—In 1909, Conradi [3] examined 162 organs from freshly slaughtered cattle and pigs; 72 of them contained micro-organisms. Bacteria were found in 42 of 63 livers, 18 of 59 muscles, 6 of 19 kidneys, and 4 of 5 lungs. The micro-organisms were both aerobic and anaerobic. The latter were present in 30 per cent of the tissues examined.

Reith [4] found that 77 per cent of 216 slaughtered hogs had bacteria in the muscle, and of these, 37 per cent were anaerobes.

Experimental Studies on the Ability of Micro-Organisms to Pass out of the Intestinal Tract into the Lymph or Blood Stream.—Arnold's [5] many contributions to the subject show that when the upper half of the intestinal tract in dogs, which is normally slightly acid, is made alkaline, the intestinal flora of the large bowel is found. Working with injection of B. prodigiosus into the duodenum, with or without accompanying egg white, he found that bacteria went into the blood stream quickly and in great numbers in the presence of egg white in the duodenum.

In the examination of mesenteric lymph glands in dogs, 50 per cent were found to contain a varied bacterial flora, which was greatly increased in obstruction of the bowel (Dr. David).

Presence of Micro-Organisms in the Urine in Patients with Focal Infections in the Mouth.—G. F. Dick and G. R. Dick [6] found that 60 per cent of patients examined by them with evident foci of infection had considerable numbers of bacteria in the urine. In a number of instances one or more of the kinds of bacteria found in the urine were isolated from the foci of infection in the mouth.

2. Dudgeon, L. S.: J. Hyg. **25**:119, 1926.
3. Conradi, H.: München. med. Wchnschr. **56**:1318, 1909.
4. Reith, A. F.: J. Bact. **12**:367, 1926.
5. Arnold: J. Hyg. **29**:82, 1931; Proc. Soc. Exper. Biol. & Med. **28**:358, 1931.
6. Dick, G. F., and Dick, G. R.: The Bacteriology of the Urine in Focal Infections, Arch. Int. Med. **19**:493 (March) 1917.

Liver Autolysis Experiments.—It has been shown that small pieces of dog's liver placed in the peritoneal cavity of dogs caused death of the animals. Ellis and Dragstedt [7] showed that a gram-positive anaerobe was present in the peritoneum of these dogs. If, however, liver from pups removed by cesarean section were placed in the peritoneum no ill effects were noted, and the culture of the liver was sterile. Andrews [8] repeated the experiments, and concluded that B. welchii probably passed through the intestinal wall and infected the liver. Later, Rewbridge [9] and Andrews, Rewbridge and Hrdrina [10] allowed bile to flow into the peritoneal cavity or injected sterile bile salts into the peritoneum, and concluded that death was not due to toxemia from bile salts but to a B. welchii infection. They also took 100 Gm. of ground autoclaved dog's muscle and implanted it into the peritoneal cavity of dogs. They found at autopsy that all had B. welchii infection. They concluded that B. welchii was normally present in dog's muscle, and that injection of sterile bile salts into the muscle would activate the B. welchii so that a fatal infection ensued.

Clinical Investigations on the Presence of B. Welchii in the Soft Parts and Peritoneum.—1. It has been frequently noted, especially during the war, that fatal gas bacillus infection was often due to B. welchii growing in symbiosis with the streptococcus.

2. The presence of B. welchii in appendicitis and peritonitis has been noted. Heyde [11] studied the anaerobic flora in 102 acutely inflamed appendixes, most of which were perforated. In 100 he found anaerobes, of which 15 per cent were B. welchii, 20 per cent anaerobic streptococci and 45 per cent small gram-negative anaerobes.

Weinberg, Prevet, Davisme and Ranard [12] stated that in the study of 160 acutely inflamed appendixes the anaerobes predominated in the gangrenous cases. Thirty-three per cent were B. welchii, 39 per cent an anaerobic gram-negative bacillus and 19 per cent anaerobic cocci.

Meleney, Harvey and Zern [13] found that in cases of perforated appendixes with diffuse peritonitis B. welchii was present in 27 per cent, streptococci in 55 per cent, and B. coli in 100 per cent. In acute non-perforated local peritonitis, B. welchii was present in 13 per cent, in acute diffuse peritonitis in 31 per cent, and in appendical abscesses in 44

7. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis in Vivo, Arch. Surg. **20**:8 (Jan.) 1930.

8. Andrews, Edmund: Proc. Soc. Exper. Biol. & Med. **27**:987, 1930.

9. Rewbridge: Surg., Gynec. & Obst. **52**:205, 1931.

10. Andrews, Rewbridge and Hrdrina: Surg., Gynec. & Obst. **53**:176, 1931.

11. Heyde: Beitr. z. klin. Chir. **76**:1, 1911.

12. Weinberg, Prevet, Davisme and Ranard: Ann. Inst. Pasteur **42**:1167, 1928.

13. Meleney, F. L.; Harvey, H. D., and Zern, H. Z.: Peritonitis, Arch. Surg. **22**:1 (Jan.) 1931.

per cent. In all of these conditions, B. coli and streptococci were present in varying percentages.

Eichhoff and Pfannensteil [14] showed that B. coli, streptococcus and Frankel's bacillus were the predominating bacteria in appendicitis. In acute appendicitis, Frankel's bacillus was present in 33 per cent.

Bacteriology of Perforated Duodenal Ulcer.—Lohr [15] found that in early perforated duodenal ulcer the peritoneal cavity contained no pathogenic micro-organisms. In 22 patients that he examined B. coli were not found up to twelve hours after perforation. Later, however, the same type of micro-organisms that are found in the colon appear in the peritoneal exudate. Anaerobes, however, are rare.

COMMENT

The experiments reported in this paper lead one to believe that in certain laboratory animals local infections from known bacteria are early changed in character by the appearance, in the lesion of other bacteria, generally B. welchii, which soon predominate over the original infection. The source of the secondary invading bacteria seems to be the local tissue, and it is probable that these bacteria were there in an inactive and nonpathogenic form until brought to life by the local infection, which created favorable conditions for their growth.

In this connection it should be noted that the culture of dog's muscle on artificial mediums failed to develop bacteria, whereas in the living animal muscle, micro-organisms growing on culture mediums created such favorable conditions for growth that the attenuated bacteria already in the muscle became activated and overgrew the bacteria used in the experiment. To what extent B. welchii gains access to the blood stream from time to time in the dog's intestinal tract and becomes seeded throughout the body tissues is not known. But some such distribution of B. welchii in dog and rabbit tissue seems probable from these experiments. Finally, it seems probable that bacteria are present in an avirulent state in animal tissue, and that they may rapidly assume a virulent character if a continuing infection develops from bacteria introduced into the tissues from without.

To what extent these findings and conclusions can be applied to infections in human tissues is, of course, a conjecture. Certain facts, however, make it an interesting speculation. There are many examples of the insidious migration and lodging of bacteria in the tissues of the human body, such as arthritis, osteomyelitis and cholecystitis. It is also known that bacteria may be dormant in tissues for long periods without producing clinical symptoms until, as a result of trauma or favorable

14. Eichhoff and Pfannensteil: Beitr. z. klin. Chir. **151**:171, 1931.
15. Lohr: Zentralbl. f. Chir. **53**:1618, 1926; Ztschr. f. Chir. **214**:103, 1929.

local conditions, they become active, as in the case of ankylosed joints following suppurative arthritis. Evidence also exists that some bacteria seem to flourish best when growing in symbiosis with other bacteria, as for instance in peritonitis or gas bacillus infection. The great variety of bacteria found in peritonitis, cholecystitis and cellulitis (as ischio-rectal abscess) offers the opportunity to consider whether some of the bacteria found in these lesions were lying dormant in the tissues where they had previously lodged and were activated by the introduction of an outside or new infection in these tissues. The presence of strepto-cocci in so many lesions may possibly be accounted for on a similar basis. It is difficult to prove such a contention; we have no direct proof, and only offer the possibility as an analogy to the experimental data on animals.

CONCLUSIONS

The introduction of bacteria on culture mediums into the tissues of certain animals results in severe infection which is due not only to the bacteria introduced but to secondary invaders, chiefly B. welchii. Experimental evidence is submitted which indicates that the secondary invading bacteria were already present in the tissue in an avirulent state but were activated to growth by the infection introduced.

The practical significance of these observations concern: 1. The importance of the death of tissue in surgical procedures acting as a favorable culture medium for the development of bacteria already present in the tissue or introduced at the time of the operation.

2. The suggested mechanism of the development of some secondary infections.

3. The increase of the virulence of B. welchii when growing in symbiosis in living tissue with pus-producing bacteria.

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DIVERTICULITIS OF THE COLON IN WOMEN

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The recognition of the clinical importance of diverticulitis of the colon is largely a development of the past two decades. Even though Virchow,[1] in 1853, described "isolated, circumscribed, adhesive peritonitis" of the colon, it was not until 1899 that Graser,[2] as the result of postmortem studies, directed attention to the association of these localized inflammatory processes with diverticula of the large bowel. In 1907, Mayo, Wilson and Giffin[3] reported five cases of diverticulitis that had been encountered at operation and emphasized for the first time the symptomatology of the disease. It was not until 1914 that the condition was recognized by roentgenologists.[4] Since that time the ever increasing number of reports of this condition in medical, surgical and roentgenologic literature has brought convincing evidence of its enlargeing clinical importance.

Diverticulitis of the colon may be defined as an inflammation of one or more diverticula, or accessory pouches, of the large bowel. The term diverticulosis is usually employed to describe the presence of asymptomatic diverticula. True diverticula of the colon are exceedingly rare and are of little clinical importance; such diverticula are congenital and represent a developmental disturbance in which the walls of the pouches are composed of mucosa, muscularis and serosa. The most common form of diverticulum is the false or acquired diverticulum, which apparently has its origin in a structural weakness of the muscularis that permits the mucosa to herniate through the divided muscular layer and form a pouch, the wall of which is made up of mucosa and serosa. Such acquired diverticula have been aptly called mucosal hernias.

The great majority of diverticula occur in the sigmoid colon. In an operative series of forty-two cases of diverticulitis of the colon reported

From the Surgical Division of the Dayton Clinic.

1. Virchow, R.: Historisches, kritisches und positives zur Lehre der Unterleibsaffektionen, Virchows Arch. f. path. Anat. u. Physiol. 5:281, 1853.

2. Graser, E.: Ueber multiple Darmdivertikel in der Flexura sigmoidea, Verhandl. d. deutsch. path. Gesellsch. 28:254, 1899; Das falsche Darmdivertikel, Arch. f. klin. Chir. 59:638, 1899.

3. Mayo, W. J.; Wilson, L. B., and Giffin, H. Z.: Acquired Diverticulitis of the Large Intestine, Surg., Gynec. & Obst. 5:8, 1907.

4. Abbe, R.: Case of Sigmoid Diverticulitis Simulating Malignancy, M. Rec. 86:190, 1914.

by W. J. Mayo,[5] sigmoid diverticula were found in thirty-six cases. Judd and Pollock [6] found diverticulitis of the sigmoid colon in 75 per cent of one hundred and eighteen cases, while Masson [7] found the colonic diverticula to be restricted to the sigmoid colon in 81 per cent of one hundred and sixteen cases. In about 20 per cent of cases, diverticula may be found in the cecum, ascending colon, transverse colon, descending colon or in the rectum.

Diverticula may vary in number from one to several hundred. In rare instances the entire colon may be studded with saccules varying in size from that of a pinhead to that of a walnut. There is no agreement as to any constant location of diverticula in their relation to the mesentery. Some writers have stated that diverticula are most commonly observed at the antimesenteric border, particularly at the point of penetration by blood vessels. As a matter of fact, diverticula have been found to occur at any point along the circumference of the wall of the large bowel. Kieth [8] expressed the opinion that diverticula result from increased intracolonic pressure, with the protrusion of sacculations of mucous membrane through weak areas in the musculature. In all probability the production of acquired diverticula is dependent on several factors. The disease occurs most commonly in obese persons past 40 years of age, who are physically inactive and who have experienced chronic constipation for many months or years. Ordinarily, chronic constipation affects the sigmoid colon to a greater degree than it does other parts of the large bowel, because the fecal current is slowest in the sigmoid flexure. It seems probable, therefore, that a combination of some or all of these circumstances is responsible for the development of diverticula. Diverticulitis is much more common in men than in women, in the ratio of approximately 2:1.

That diverticulosis and diverticulitis are much more common than is generally believed is illustrated by the frequency with which diverticula are discovered accidentally as the result of routine roentgen studies. At Washington University, Larimore [9] found definite evidence of diverticulosis in fifty five (1.65 per cent) of 4,408 patients who were subjected to roentgen studies of the intestinal tract. Spriggs and Marxer [10] found

5. Mayo, W. J.: Diverticulitis of the Large Intestine, J. A. M. A. **69**:781 (Sept. 8) 1917.

6. Judd, E. S., and Pollock, L. W.: Diverticulitis of the Colon, Ann. Surg. **80**:425, 1924.

7. Masson, J. C.: Diverticulitis of the Large Bowel, Canad. M. A. J. **11**:106, 1921.

8. Kieth, A.: Diverticula of the Alimentary Tract of Congenital or of Obscure Origin, Brit. M. J. **1**:376, 1910.

9. Larimore, J. W.: Diverticulitis of the Large Intestine, J. Missouri M. A. **22**:129, 1925.

10. Spriggs, E. I., and Marxer, O. A.: Intestinal Diverticula, Brit. M. J. **1**: 130, 1926.

one hundred cases of diverticulosis in 1,000 roentgenologic examinations of the large bowel.

DIAGNOSIS AND TREATMENT

Diagnosis.—Diverticulitis may manifest itself as an acute or chronic disease. When the disease exists in the chronic form, acute exacerbations are common. Ordinarily the patient will complain of vague, intermittent pain, occasionally cramplike in severity, in the lower left abdominal quadrant. Occasionally the pain is most pronounced in the lower mid-abdominal region. Many patients will complain of bladder symptoms, notably frequency and tenesmus. If the abdominal wall is thin, it is usually possible to palpate a tender, ropelike, hard, nodular sigmoid colon. The sacculations usually become filled with fecal material which becomes inspissated and often impregnated with calcium salts, forming rocklike fecaliths. These scybalous masses may cause pressure atrophy and erosion of the intestinal wall, with the development of perforation, abscess or localized or generalized peritonitis. In some instances fistulas may develop into the urinary bladder or through the skin. The development of large inflammatory masses with or without perforation may produce angulation and obstruction. In rare instances adenocarcinoma may develop in the diverticulum, probably as a result of prolonged irritation.

Acute diverticulitis usually produces the symptomatology of left-sided appendicitis. The severe sudden abdominal pain is usually generalized at the abrupt onset of illness, but becomes localized in the region of the suppurative diverticulitis. These symptoms are accompanied by localized tenderness, muscle spasm, fever and leukocytosis; nausea and vomiting may occur. While the suppurative process remains restricted to the diverticulum, the fever and leukocytosis are usually of the mild degree seen in acute appendicitis. Extensive ulceration of the mucosa of the diverticulum is rare, so that it is unusual to find blood in the stool.

Unless the symptoms indicate that immediate operation is advisable, roentgen studies should be made. The roentgenographic appearance of diverticula of the large bowel is usually characteristic and diagnostic. If the saccules are filled with fecal matter, it is often impossible to outline the diverticula with the barium mixture. A ragged, spastic, "saw-tooth-like" appearance of the large bowel is highly suggestive and should invite further roentgen studies.[11] If roentgenograms are taken from twenty-four to seventy-two hours after the opaque meal is given, the residue of barium will frequently outline the pockets after the lumen of the bowel has been emptied.[12]

11. Mackoy, F. W.: Family Diverticulosis of the Colon, Radiology **7**:498, 1926.
12. Enfield, C. D.: Diverticulosis and Diverticulitis of the Colon, Am. J. Roentgenol. **12**:242, 1924.

Treatment.—The mere presence of symptomless diverticula does not warrant surgical intervention. Surgical treatment should be confined to acute diverticulitis or to the complications of chronic diverticulitis. The most common complications are perforation, with the development of localized or generalized peritonitis, formation of abscesses, intestinal obstruction due to a large inflammatory mass, fistulas between the involved area and the bladder, intestine or skin, secondary abscess of the liver and a malignant condition. Perforation of a diverticulum during an acute attack is rare. Ordinarily, the perforation does not occur into the free peritoneal cavity, because the preexisting inflammatory reaction usually fixes the sigmoid to loops of the small intestine or to the parietal peritoneum or anterior abdominal wall. Consequently, formation of abscess is the most common complication.

The development of acute diverticulitis requires surgical treatment. If it is found that localized peritonitis or abscess has developed, the area should be drained, and the loop of bowel containing the infected area should be drawn through a split-muscle incision. I have found it unwise to excise or open this loop because of the danger of rupture of the diverticulum and the escape of fecal material. If the diverticulum should rupture following its withdrawal from the abdominal cavity, little or no harm results. Hot boric acid dressings should be applied to the exposed loop of infected bowel until the infection has become inactive. After the inflammatory process has entirely subsided, it is possible to release the loop of bowel and place it beneath the abdominal muscles, external to the peritoneum. The incision is then closed without drainage. If the diverticulitis does not subside, a Mikulicz resection usually yields the best results.

On opening the abdomen it may be difficult in certain instances to distinguish between carcinoma of the large bowel and diverticulitis. The regional lymph-nodes are usually enlarged and firm in the presence of diverticulitis, as well as of carcinoma. In such cases a rapid microscopic examination of the tissue should be carried out. If any doubt exists as to the presence of carcinoma, radical resection is indicated. The loop of bowel containing the neoplasm can usually be delivered through the abdominal incision, and a Mikulicz resection can then be performed.

REPORT OF CASES

One purpose of this undertaking is to present the pertinent clinical findings in four cases of diverticulitis of the colon, three of which presented pelvic symptoms that led to confusion with gynecologic conditions.

CASE 1.—Mrs. N. A., aged 52, an obese housewife, presented herself on July 1, 1930. With the exception of chronic constipation, she had enjoyed excellent health until four weeks before this time. The menstrual history had been entirely uneventful prior to the onset of the present illness. Four weeks previously the patient began to experience continuous pain in the lower part of the abdomen.

which became localized in the right lower quadrant. About one week following the development of the abdominal pain the patient began to have continuous vaginal bleeding, which gradually increased in intensity. She had lost 30 pounds (14 Kg.) in weight during the four weeks of illness. On examination, the temperature was found to be 100 F., with a heart rate of 92. The skin and mucous membranes showed marked pallor. The tongue was dry and parched. Examination of the head, neck and chest revealed no abnormalities. A large nodular mass was found in the center of the lower part of the abdomen, which extended 3 cm. above the umbilicus. The mass was exquisitely tender on pressure. On vaginal examination a large, tender, fixed mass was found to fill the entire pelvis.

Hematologic studies revealed 2,630,000 red blood cells per cubic millimeter and 2,300 white blood cells, with 93 per cent neutrophilic polymorphonucleosis. The estimation of hemoglobin was 45 per cent (Dare). Chemical analysis of the blood showed: creatinine, 2 mg. per hundred cubic centimeters; urea nitrogen, 17 mg.; blood sugar, 357 mg., and blood chlorides, 505 mg. The Wassermann and Kahn tests of the blood were negative. An analysis of the urine revealed a large amount of albumin and 2.1 Gm. of sugar per hundred cubic centimeters, with acetone and diacetic acid. The microscopic examination revealed a large number of separate and clumped pus cells; there were no red blood cells and no casts.

The patient was given medical treatment, which consisted of regulation of the diet, insulin, forced fluids and transfusions. During the following week, the blood sugar was restored to the normal level, and three transfusions were given. Laparotomy was done on July 8, 1930, with the preoperative diagnosis of multiple fibromyomas of the uterus. A large nodular uterus, containing multiple fibromyomas, was found, with an orange-sized abscess between the omentum and the fundus of the uterus, which extended into the left broad ligament and involved the sigmoid colon. This colon showed multiple diverticula. The abscess originated in one of the diverticula. Supravaginal hysterectomy, bilateral salpingectomy and appendectomy were done. The loop of sigmoid colon containing the infected diverticulum was brought to the outside of the abdomen through a split-muscle incision. Dressings of hot boric acid were repeatedly applied to the exposed portion of the sigmoid colon, and after two weeks the inflammatory process had entirely subsided. Three days after the sigmoid had been withdrawn from the abdomen, the diverticulum ruptured and discharged purulent fecal material for five days. After the inflammatory process had subsided, the sigmoid was detached from the skin and placed beneath the left rectus muscle, external to the peritoneum. The convalescence was uneventful, and the patient was discharged from the hospital on Aug. 17, 1930. She has since regained her normal weight and has been in excellent health.

CASE 2.—Mrs. D. K., an obese housewife, aged 54, was first seen on Nov. 3, 1928. Her health had always been excellent. She had experienced chronic constipation for many years. The menopause had occurred six years previously. Three weeks before admission to the clinic she experienced a sudden, severe pain in the lower left abdominal quadrant, which was relieved following an enema. Since that time the pain had persisted to a less marked degree in the same region. Occasionally it became generalized over *the entire abdomen*, and she became nauseated. The general physical examination revealed nothing of importance except in the abdomen and pelvis. A tender mass, the size of a lemon, was palpable in the lower left abdominal quadrant. There was *no rigidity* of the muscle. On vaginal examination the uterus was found to be small and tender on deep pressure. There was a tender, palpable mass, the size of an orange, in the region of the left broad ligament.

The temperature was 99.6 F., with a pulse rate of 95. Hematologic studies revealed a slight degree of secondary anemia, with no leukocytosis. The Wassermann and Kahn tests of the blood were negative. Urinalysis gave negative results.

On Nov. 4, 1928, laparotomy was performed, with the preoperative diagnosis of pelvic tumor. A large orange-sized, fluctuant mass was encountered at the rectosigmoid junction. About 3 inches (7.6 cm.) above this mass and connected with the sigmoid colon was a similar mass about 5 cm. in diameter. The gross appearance strongly suggested carcinoma of the sigmoid. The first stage of a Mikulicz operation was performed. The pathologist reported multiple diverticula, with no evidence of malignant transformation. Hot boric acid dressings were applied to the intestine; fourteen days later it was placed beneath the rectus muscle, external to the peritoneum, and the abdominal wound was closed.

On Nov. 12, 1928, the patient was discharged from the hospital with a small draining sinus, which closed within the next two weeks. On Feb. 27, 1930, a barium enema was given; the roentgenograms revealed a normal colonic outline, except for the presence of several small pea-sized diverticula near the splenic flexure. At present the patient is in excellent health.

CASE 3.—Mrs. M. S., a housewife, aged 48, presented herself for clinical study on Jan. 31, 1931. The chief complaint was abdominal pain. During the summer of 1930, the patient had experienced severe "bearing down" pains in the abdomen and pelvis. Her previous health had been good, except for an almost constant dull headache that had persisted for years. Coincident with the development of the abdominal pain, urinary frequency and nocturia developed. The patient was unable to empty the bladder completely. These symptoms persisted until November, 1930, when they abruptly ceased. The previous good health was regained, except for constant backache.

On the day before admission to the clinic acute pain developed in the lower part of the abdomen, associated with marked urinary frequency. The pains were sharp and cramping. She had always been more or less obese and had experienced no recent loss in weight. There had been no menstrual difficulties prior to the menopause, which occurred at 44 years. She had four healthy children.

The results of the general physical examination were entirely negative, except for the pelvic examination. The uterus was markedly retroflexed; there were no palpable tumor masses.

Studies of the blood, the Wassermann and the Kahn reactions and urinalysis gave entirely negative results.

In the absence of other findings it was concluded that the relaxation of the pelvic floor, together with the marked retroversion of the uterus, had caused protrusion of the cervix into the bladder; this in turn had caused urethral obstruction.

On Feb. 21, 1931, laparotomy revealed marked retroversion of the uterus and a lemon-sized mass in the anterior wall of the large intestine, at the rectosigmoid junction. Ventral fixation of the uterus was done, together with ligation of the fallopian tubes and removal of the mass in the rectosigmoid wall. This mass was found to contain four cherry-sized diverticula, each containing masses of inspissated feces. There was no evidence of malignancy. A small fecal fistula developed on Feb. 26, 1931; it gradually closed during the next two weeks. The operation was followed by complete relief of symptoms. The patient has experienced excellent health since the time of operation.

CASE 4.—Miss J. F., a school teacher, aged 55, was first seen on March 28, 1931. Two years previously, 100 Gm. of radium, with a brass screen, had been placed in the uterine cavity for twenty-four hours, in order to control uterine hemorrhage due to the presence of a submucous fibromyoma. In January, 1930, a

complete diagnostic survey was carried out. The patient's complaints at that time were marked constipation and pain in the lower part of the back, with a constant dull headache and insomnia. The pain in the back frequently radiated around to the right side of the abdomen.

The results of complete physical and laboratory examinations at this time were essentially negative, except that a barium enema revealed several small diverticula in the sigmoid colon.

On March 28, 1931, the patient experienced a sudden, sharp, generalized abdominal pain that gradually localized itself in the right lower abdominal quadrant. The onset of the pain was followed by nausea and vomiting. The temperature was 101.4 F., with a pulse rate of 105. The results of a general physical examination were negative, except for the presence of tenderness and rigidity of the muscles over the lower right abdominal quadrant. There were no palpable tumor masses. The blood picture showed a white blood cell count of 14,500 with 94 per cent polymorphonuclear neutrophils. Urinalysis gave negative results.

A diagnosis of acute appendicitis was made, and the abdomen was opened through a split-muscle incision. The cecum was found to lie in the pelvis, and the appendix was found to be normal. At the upper end of the incision a firm, spherical mass, 8 cm. in diameter, was palpated. When this mass was withdrawn from the abdomen, a small amount of pus escaped. The mass was found to be the hepatic flexure of the colon, with multiple small diverticula protruding from it. The mass was left outside of the abdomen, and dressings of hot boric acid were applied. Several of the diverticula ruptured and drained fecal material for several days. The inflammatory process subsided in about two weeks, after which the colon was replaced beneath the abdominal muscles, external to the peritoneum. The wound healed rapidly, and the patient has experienced good health since the operation.

SUMMARY AND CONCLUSIONS

1. Diverticulitis of the colon is a much more common disease than is generally appreciated.

2. Diverticulitis of the mobile sigmoid colon may produce symptoms of pelvic disease. In three of the four cases that form the basis of this thesis, the symptoms led to confusion with gynecologic conditions.

3. In one instance, reported herewith, the symptoms of acute diverticulitis closely simulated those of acute appendicitis.

4. Acute diverticulitis and the complications of chronic diverticulitis require surgical treatment. The withdrawal of the loop of bowel containing the infected diverticula through a split-muscle incision in the anterior abdominal wall, followed by the application of hot boric acid dressings until the inflammatory process has subsided, has yielded the best results in my experience. After the inflammation has subsided the loop of bowel may be released and placed beneath the abdominal muscles, external to the peritoneum. In the absence of intestinal obstruction or of evidence of carcinoma, it is rarely necessary to perform a Mikulicz resection.

FIFTIETH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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MISCELLANEOUS

Echinococcus Disease of the Bone.—Coley[24] reported 2 cases of echinococcus disease of the bone. Both involved the bones of the pelvic girdle. In both cases the diagnosis was arrived at late in the disease and after the patients had been treated with high voltage roentgen therapy without benefit. In each case the diagnosis was made by biopsy. One patient is still alive, but the other died of complications following biopsy. Two forms of treatment are discussed. One consists in evacuation of the large cystic cavity and treatment with phenol or formaldehyde in the hope of producing fibrosis and subsequent obliteration of the cavity. The other, more ideal one consists in wide excision or amputation of the bone involved. The author stated that only 3 cases of osseus hydatid disease had been reported in this country up to 1930.

Roentgen Signs of Infantile Scurvy.—Kato[25] discussed the various so-called pathognomonic roentgen signs of infantile scurvy. The white

24. Coley, B. L.: J. Bone & Joint Surg. **14**:577, 1932.
25. Kato, K.: Radiology **18**:1096, 1932.

line in the metaphyseal area of the long bones seen in scurvy is also found in lead poisoning, phosphorus poisoning and other diseases. The contiguous area of diminished density of bone is likewise not pathognomonic. The sharp hairline outline of the epiphysis, while always present, is found in some other lesions. From a roentgen standpoint all of the so-called pathognomonic signs of scurvy must be correlated, and subperiosteal hemorrhage must be present if one is to make a positive diagnosis.

[ED. NOTE.—This article merits careful reading. The old conception of certain findings in certain diseases as classic must again be modified by reasoning and clinical observation.]

Diagnosis of Amyloid Disease.—In 1923, Bennhold discovered that an intravenous injection of aqueous solution of congo red could be used as a test for the presence of amyloid disease. Amyloid material absorbed the congo red, and the percentage decrease of the dye content of the serum over a period of one hour was estimated colorimetrically. In the normal person, from 10 to 20 per cent was found to have disappeared; in patients with amyloid disease, the diminution was between 30 and 100 per cent. Wallace [26] tried the test on 30 patients. It confirmed the diagnosis of amyloid disease in 15 of 17 patients clinically suspected of having the disease. Wallace argued that the test gave a quantitative result, and therefore was superior to Waldenstrom's liver puncture test, besides being less drastic.

Kienböch's Disease.—Mouat, Wilkie and Harding [27] studied 12 patients with Kienböch's disease. In 6 the semilunar bone was excised; of these, 4 resumed their former work, 1 did light work, and 1 could not be traced. In the other 6 the semilunar bone was not excised; of these, 1 resumed his former work, 1 did light work, and 4 remained unable to work. After removal of the semilunar bone, pain was relieved, and the outlook as regards recovery of function was excellent in the cases in which the prognosis was not impeded by a question of litigation. There was, however, some loss of range of movement, which, as a rule, diminished the wage-earning capacity.

Subchondral Focal Necrosis of the Third Metacarpus.—Dietrich [28] reported 7 cases of necrosis of the distal end of the third metacarpal bone which he believed were examples of aseptic necrosis. This would

26. Wallace, J. E.: Lancet **1**:391, 1932.

27. Mouat, T. B.; Wilkie, J., and Harding, H. E.: Brit. J. Surg. **19**:577, 1932.

28. Dietrich, H.: Arch. f. klin. Chir. **171**:555, 1932.

constitute a syndrome comparable to Köhler's disease of the second metatarsus. The clinical signs were mainly pain, local swelling of the affected joint and a sense of tightness on making a fist. Histologic examination of the bone of the first patient, a girl of 15 years, yielded a pathologic picture which fitted in well with that of aseptic necrosis. Some of the other cases were open to question as to the assuredness of the diagnosis. The last patient presented deformity of the metacarpus, broadening vacuolization and free body formation. Unfortunately no section of tissue was available in this instance.

Osteochondritis Deformans Contrasted with Osteochondritis Deformans Juvenilis.—In discussing hypertrophic arthritis and the changes in the joints associated with coxa plana (Legg's disease), Lang [29] concluded that although there are factors involved in the former, such as age, vascular changes and perhaps systemic disease, that are not present in the latter, trauma is an important causative factor in both, and that the disease originates after damage to the articular cartilage. This loss of elasticity removes the protection that the normal cartilage affords to the subchondral bone against functional and mechanical influences.

Disturbances of Consolidation After Orthopedic Osteotomies.—In 621 osteotomies performed during a ten year period, 8 cases of delayed union were encountered by Brandes.[30] Of these, 3 ended as true pseudarthrosis. In all but 1 case (pregnancy) local causes were present. Most of the disturbances occurred following osteotomies of the leg. No difficulty was encountered after osteoclasis.

TRAUMATIC INJURIES TO THE JOINTS

Traumatic Dislocation of the Hip.—Platt,[31] after remarking on the fact that traumatic dislocation of the hip is usually reduced without special difficulty and results in perfect function of the joint, recorded 4 cases with complications, as follows: (1) Fracture of the acetabular rim with extrusion of the loose bony fragment *per vaginam*: result, perfect. (2) Involvement of the sciatic nerve and myositis ossificans, necessitating excision of the head of the femur. Severe irritative signs developed as the sciatic nerve was recovering. The ultimate fate of the patient was unknown. (3) Chip fracture of the head of the femur and fracture of the acetabular margin, giving rise to two loose bodies. These bodies were removed, and the function of the hip joint was perfect, but only partial recovery occurred in the sciatic nerve, which was also damaged at the time of the original accident. (4) Chip fracture

29. Lang, F. J.: J. Bone & Joint Surg. **14**:563, 1932.
30. Brandes, M.: Arch. f. klin. Chir. **170**:408, 1932.
31. Platt, H.: Brit. J. Surg. **19**:601, 1932.

of a portion of the head of the femur giving rise to a loose body. This body was removed, and the result was perfect.

Injuries to the Tibial Collateral Ligament of the Knee Joint.—Regele[32] stated that injury to the tibial collateral ligament of the knee joint is the commonest injury in this region. The injury occurs through bending, which separates the upper and lower joint surfaces; through stretching, which can be of several types, and through side bending, which produces an increased valgus. In the milder cases there is a sharp pain immediately or pain only after a number of hours. The knee is usually held in slight flexion; there is some swelling on the inner side of the knee. In the more severe cases hemorrhage into the joint of the knee is the rule; pain is not as definitely localized as in the milder cases. Complete extension of the knee is restricted chiefly. Lateral stretching of the knee causes pain referred to the tibial collateral ligament. Sometimes there is an abnormal amount of lateral motion. These severer injuries are frequently associated with changes in the internal meniscus. The differentiation between an injury to the meniscus alone and an injury to the tibial collateral ligament is shown by more severe pain immediately in the former and slowly developing pain in the latter. The localization of the pain is helpful. Pain occurs on attempted adduction of the knee only when the ligament is affected. Hemorrhage into the joint is usually the result of an injury to the ligament. There is greater hindrance to extension when the meniscus is injured. Roentgenograms often show bony spicules torn off in injury to the tibial collateral ligament, while they show no changes in the meniscus. Severe tears may lead to an unstable knee and to arthritic changes. Bowing sometimes develops, more so in the heavy patient. Later limitation of motion may develop from faulty healing of the ligament. For treatment the author advises fixation of the knee in extension in a plaster cast. Hemorrhages should be aspirated immediately, and a pressure bandage applied before the cast is put on to avoid a recurrence of the hemorrhage. Fixation should be continued for from four to eight weeks, according to the severity of the injury, the constitution and the age. In young persons from one to two weeks is often sufficient. Walking in the cast is permitted immediately. Bad results occur from improper fixation, fixation in flexion or hyperextension, failure to remove the hemorrhage and early massage, which tends to increase the bleeding.

Tennis Elbow.—Carp[33] advocated a new form of treatment for epicondylitis (tennis elbow). The treatment consists in applying firm

32. Regele, H.: München. med. Wchnschr. **79**:1474, 1932.
33. Carp, L.: Tennis Elbow (Epicondylitis) Caused by Radiohumeral Bursitis: Anatomic, Clinical, Roentgenologic and Pathologic Aspects, With a Suggestion as to Treatment, Arch. Surg. **24**:905 (June) 1932.

pressure with the thumb to the region of the bursa over the radio-humeral joint. Such pressure is maintained for two or three minutes until it is felt that the bursa has been ruptured and its contents allowed to escape into the surrounding tissues. In some cases the relief from pain is striking. The anatomic, clinical, roentgenologic and pathologic aspects of the condition were reviewed, and the details of 8 cases were given. Four of the patients were treated by applying digital pressure on the bursa. All recovered almost immediately, and there were no recurrences. One patient was treated by operation, and the others were given physical therapy, and splinting was applied.

OPERATIONS ON THE BONE, JOINT AND TENDON

Preliminary Implantation of Bone in Pseudarthrosis.—Mayeda [34] applied the method proposed by Axhausen in 1928 to infected pseud-arthroses. It is of value when one wishes to save the time which ordinarily is permitted to elapse between the healing of an infected pseudarthrosis and the date when a bone graft operation can be performed. The infected pseudarthrosis is drained and permitted to heal. Soon after healing, possibly even while a granulating area persists, a tibial or preferably a costal segment covered with periosteum is implanted in the healthy soft tissues immediately adjacent to the site of future bone grafting. This graft is permitted to develop a blood supply. At the next step, the graft is exposed over one aspect and brought in contact with the freshened pseudarthrosis and fastened in place with wire as a massive onlay graft. If infection develops, it obviously will not destroy such a vascularized onlay graft.

Dupuytren's Contracture.—Davis [35] reviewed the results of the treatment of Dupuytren's contraction in 42 cases, as follows: Excision of fascia was performed in 31 cases, with 12 perfect results, 10 partial returns of the contracture, 3 complete returns of the deformity and 6 anatomically perfect results that were functionally useless on account of painful scar, digital anesthesia or both, causing total incapacity. Multiple subcutaneous division was employed in 8 cases, with 6 perfect results, 1 partial return of the contracture and 1 complete return of the contracture. Injection of fibrolysin was tried in 3 cases, with no perfect results, 2 partial returns of the contracture and 1 complete return of the contracture. Davis concluded that as the guarantee of cure remained far from certain even following major operative procedures, the minor operation of multiple subcutaneous fascial division should be adopted, and repeated if necessary.

34. Mayeda, T.: Deutsche Ztschr. f. Chir. **236**:159, 1932.
35. Davis, A. A.: Brit. J. Surg. **19**:539, 1932.

[ED. NOTE.—Some of the editors take exception to the author's conclusions. Excellent results can be obtained by thorough excision of the contracted tissue, but in some instances this must be followed by plastic operations to close defects in the skin. Successful results by this method have been reported by many authors.]

Approach to the Anterior Portion of the Elbow Joint.—Gerlach[36] reported the end-results of 28 operations on the anterior portion of the elbow joint, using the operation devised by Läwen.[37] The operation was performed through an anterior midline incision over the elbow joint; the tendons of the biceps and the brachialis muscle were split. This operation was found particularly useful in the removal of foreign bodies from the anterior compartment of the elbow joint, and in the open reduction of fractures with anterior displacement of fragments. The author stated that there was no danger of injury to the nerve in this operation, and that the only blood vessel encountered was the medial cubital vein, which was ligated in each instance. For foreign bodies much displaced ulnad, a small transverse incision in the longitudinally split capsule gave adequate exposure. In the latter operations the joint capsule was not sutured; the author believed that the drainage which this permitted was advantageous. Primary healing was observed in all cases. Physical therapy was begun in from eight to ten days. In 19 cases in which the end-results were obtainable, there were 10 excellent results and 1 ankylosis.

Recurrent Inferior Radio-Ulnar Dislocation.—Eliason[38] described a new operation for recurrent inferior radio-ulnar dislocation. A strip of fascia was passed around the lower end of the ulna, and then both ends of the fascia were carried through a drill hole in the radius running from the posterior and ulnar aspect forward and outward to penetrate the outer radial cortex about 1¼ inches (3.14 cm.) above the radial styloid. It was necessary to perform a secondary operation on the same wrist six months later because of a severe strain produced by sharply supinating the wrist. At the second operation the anterior and posterior radio-ulnar ligaments were plicated to take up the relaxation of this structure. In addition, a portion of the ulnar attachment of the pronator quadratus muscle was shifted distally and sutured over the joint as an additional splint. The author recommended that both procedures be carried out at one sitting.

[ED. NOTE.—This seems to be a rather elaborate procedure. One should consider whether subperiosteal resection of the lower end of the ulna as advocated by Darrach would not give a better functional result.]

36. Gerlach, K.: Beitr. z. klin. Chir. **155**:589, 1932.
37. Läwen, A.: Arch. f. klin. Chir. **162**:521, 1930.
38. Eliason, E. L.: Ann. Surg. **96**:27, 1932.

Operative Fusion of Unstable or Flail Knee in Poliomyelitis.—Cleveland [39] presented a study of 90 patients with infantile paralysis on whom operative fusion for flail legs had been performed. The youngest patient was 9 years of age; the oldest, 33 years; the average age was from 15 to 16 years. In practically all cases the reason for fusing the joint was to obviate the use of a brace. Practically no increase in shortening was obtained after operation, it being on an average 2 inches (5 cm.) as compared to 1¾ inches (4.37 cm.) before operation. In all but 2 patients fusion was obtained at the first operation. Flexion and knock-knee deformity occurred in 15 patients following the operation and were due to hamstring contracture and ununited epiphyses. These complications required secondary corrective operations. In 85 per cent of the patients good cosmetic and functional results were obtained.

FRACTURES

Fractures in and Near the Ankle Joint.—Miller,[40] in discussing fractures in and about the ankle joint, stated that reduction is usually quite easy if undertaken in the first few hours after the fracture occurs. The most satisfactory anesthesia is from 10 to 15 cc. of a 2 per cent solution of procaine hydrochloride injected into the hematoma about the fracture. It is most important to secure the normal relationship of the articulating surfaces of the ankle joint. Immobilization is maintained by a plaster cast which is bivalved for physical therapy in one week. Weight bearing is not permitted until firm union of the fracture has occurred, which is usually in eight weeks.

Fractures and Epiphyseal Separation at the Ankle.—Bishop [41] reviewed the classification of fractures of the ankle proposed by Ashhurst and Bromer, i. e., according to the mechanism of production, and classified 300 cases in this way: (*A*) fractures caused by external rotation, 54.4 per cent; (*B*) fractures caused by abduction, 26.3 per cent; (*C*) fractures caused by adduction, 14 per cent; (*D*) fractures caused by compression, 4 per cent, and (*E*) fractures caused by direct violence, 1.3 per cent. His percentages in the various groups were almost identical with those given by Ashhurst. He then reviewed 32 fractures associated with separation of the lower tibial epiphysis and classified them in the same way: (*A*) 18.7 per cent, (*B*) 12.5 per cent, (*C*) 53.1 per cent, (*D*) 12.5 per cent and (*E*) 3.2 per cent. There were incomplete data on the end-results, indicating that deformities of growth from injury to the epiphysis were rare.

39. Cleveland, M.: J. Bone & Joint Surg. **14**:525, 1932.

40. Miller, O.: Kentucky M. J. **30**:407, 1932.

41. Bishop, P. A.: Am. J. Roentgenol. **28**:49, 1932.

Fractures of the Shafts of the Tibia and Fibula.—Jones [42] described a new type of apparatus for reducing fractures of the tibia and fibula. It consisted essentially in a thigh support which could be fastened to any table over which the leg hung at a right angle. A pin was passed through the os calcis; a stirrup was fastened to the pin, and the stirrup was then fastened to a traction bar, counteraction being gained against the thigh support. As traction was maintained, alinement was perfected by manipulation of the fragments. A nonpadded cast was then applied from the toe to the tibial tubercle. As the plaster dried, the knee was straightened to an angle of 20 degrees of flexion, and the plaster was carried to the groin.

Fractures of the Shafts of the Long Bones.—Schaanning [43] reviewed the treatment of 260 fractures of the shaft of the long bones between 1919 and 1928 at the Rikshospital, Oslo, Norway. Of these fractures, there were 113 in the lower leg, 89 in the thigh, 30 in the upper arm and 28 in the lower arm; 46 were compound fractures. Eighty patients were treated by operation, and in the remainder the fractures were reduced by manipulation. Operations were performed most frequently on the forearm, in 53.5 per cent of this series. Operation was usually performed in the first or second week after the injury. The indications for operative intervention were: (1) interposition of muscle or nerve, (2) possibility of injury to the blood vessels, (3) irreducible dislocation, (4) multiple fractures in the shaft of a bone, (5) danger of fusion of two adjacent bones and (6) failure to unite in a reasonable length of time. Operative reduction was undertaken on all fractures of the patella and olecranon. The period of convalescence averaged seven months in the nonoperative cases and ten and three-fourths months for the patients who were operated on. The methods of operative reduction were as follows: plating with the Lane or Lambotte plate, replacement of the fragments, encircling by the Parham band, wire suture, use of an ivory peg in 1 case and bone grafting in 1 case. The author believes that operative intervention is an admirable supplement when nonoperative manipulation fails. The best results were obtained when operative intervention was undertaken early. Compound fractures were an exception to this, since early operation often caused widespread infection. Operations were unusual on children under 10. In elderly patients the general condition of the patient was of more importance than the age. In operative fixation the author found the Lane plate the most satisfactory measure. He did not believe that the foreign body hindered bony union. There were 2 deaths, 1 probably due to fat embolism. Infection occurred after operation in 8 patients; 7 of these had com-

42. Jones, Robert: J. Bone & Joint Surg. **14**:59, 1932.
43. Schaanning, C. K.: Acta chir. Scandinav. **70**:1, 1932.

pound fractures. In a few cases (number not given) the Lane plate had to be removed because of persistent tenderness.

Fractures of the Neck of the Femur.—Gill [44] presented an excellent summary of the various methods of treatment of fractures of the femoral neck and deplored the fact that it is impossible to compare statistics because in some clinics cases are selected and in others they are not. He dealt with the more common methods of closed and open reduction and evaluated each fairly. He also discussed the treatment in cases of nonunion. He held that in certain cases operative fusion of the hip gives the best results.

Autogenous Bone-Graft Peg in Fresh Fractures of the Femoral Neck.—Albee [45] described his technic for the open reduction and pegging with an autogenous bone graft of ununited and fresh fractures of the femoral neck. The author stated that as nonoperative methods had shown such poor results and as the operative management was not tedious or hazardous, all fresh fractures of the femoral neck should be treated by autogenous bone pegging. This procedure was stated to give excellent results.

[ED. NOTE.—We believe that the treatment of fractures of the neck of the femur represents a complex problem. Operative treatment is permissible in the hands of good surgeons, but it has not yet been proved that better results are obtained than by the Whitman method of treatment.]

Treatment of Compression Fractures of the Vertebrae by Roger's Frame.—Mitchell [46] advocated the use of Roger's frame in treating compression fractures of the spine. Patients were kept recumbent in hyperextension after reduction; then a brace was worn for from three to six months longer. Reduction was sometimes accomplished one month after injury. Laminectomy was indicated only in the presence of neurologic findings and a positive Queckenstedt test.

Fractures of the Cervical Vertebrae.—Ten cases of fracture of the cervical vertebrae were reported in detail by Laesecke.[47] Conservative treatment was used even when injuries of the cord were present. Not infrequently complete healing took place. He warned against too early resumption of weight bearing on the injured spine.

Fractures of the Pelvis.—Leadbetter [48] discussed the treatment of fractures of the pelvis, basing his conclusions on a study of 100 cases. He stated that no one type of treatment was applicable to any type of

44. Gill, A. B.: Ann. Surg. **96**:1, 1932.
45. Albee, F. H.: California & West. Med. **37**:1, 1932.
46. Mitchell, J. I.: South. M. J. **25**:473, 1932.
47. Laesecke, M.: Deutsche Ztschr. f. Chir. **236**:329, 1932.
48. Leadbetter, G. W.: South. M. J. **25**:742, 1932.

pelvic fracture; each represented a problem in itself. The aim in each case was to bring about as perfect a restoration of the pelvic ring as possible. Only in this way could the late sequelae resulting chiefly from faulty body mechanics be avoided. The author found that a fracture of one or both pubic rami was the commonest type of fracture. Fractures of the upper third of the iliac crest were next most common. Separation of the sacro-iliac joints with displacement of the ilium was seen in 10 per cent of the cases. It was noticed that when multiple fractures occurred they all tended to be in the straight line. The author found congenital anomalies of the lower part of the spine or the pelvis in 67 per cent of the cases, but he was unable to state whether they were a predisposing factor in the causation of the fractures. The author used suspension-traction most commonly. Comfort and easy reduction of the fractures were observed in almost all of the patients so treated. In cases in which reduction was not accomplished in forty-eight hours, skeletal traction was used. Traction was continued for six weeks, and the patient was kept on a plaster board for two weeks more. Weight bearing was permitted in ten weeks.

RESEARCH

Effect of Parathyroidectomy and the Administration of Parathormone on Bone Repair.—Dragstedt and Kearns [49] excised a small segment of bone from the femur in 20 dogs and noted that the rate of repair was quite uniform unless distemper or diarrhea developed. On an additional 22 dogs thyroparathyroidectomy was performed after the femoral defect was produced. The development of tetany was controlled by the administration of calcium. Thirteen dogs did not survive the necessary sixty days of observation. In the 14 dogs which remained in comparatively good health and had received from ½ to 1½ units of parathormone per kilogram per day, the rate of healing of the femur was essentially the same as in the control series.

Intrinsic Circulation of the Vertebral Body.—Wagoner and Pendergrass [50] investigated the circulation of the blood within the vertebral body in the lumbar spine. The chief blood supply was from the lumbar arteries, the branches of the abdominal aorta. On each side of the vertebral body there was an anterolateral and a smaller lateral artery. A dorsal branch sent many small arteries directly into the bone. This dorsal artery divided at the intervertebral foramen into a spinal branch and a muscular branch. Each vertebral body was drained by four venous trunks, one vein leaving from each side of the body and two

49. Dragstedt, C. A., and Kearns, J. E., Jr.: Experimental Study of Bone Repair: Effect of Thyroparathyroidectomy and of the Administration of Parathormone, Arch. Surg. **24**:893 (June) 1932.

50. Wagoner, G., and Pendergrass, E. P.: Am. J. Roentgenol. **27**:818, 1932.

from the foramen in the center of the posterior vertebral wall. The lateral veins emptied into the lumbar veins, and the posterior veins emptied into the anterior longitudinal meningorachidian veins. The vertebrae were found to contain much blood, which had a sluggish rate of flow. There was a large venous reservoir in the midportion of the vertebral body. Here the normal venous wall was replaced by a single layer of flattened endothelial cells. The large venous channels probably played a rôle in the formation and destruction of blood; they removed and destroyed bacteria and were a factor in the localization and extension of disease processes in the vertebrae.

Roentgen Spectrographic Investigation of the Crystalline Structure of Bone.—Henschen, Straumann and Bucher [51] found that roentgen rays might be used like visible light to study the structure of material by the spectra produced. Such studies had been performed by the authors, bone being used. Both normal and pathologic bones were subjected to study. The significant findings were the verification of the crystalline structure of the inorganic salts of the bone. The organic portions of bone also show evidence of crystalline structure. The two portions of bone, the salts and the fibrils, exhibited absorption in their relationship. Also, since the character of bone changed materially with advancing years, the authors suggested that the age of bone might be approximated from spectrographic plates.

51. Henschen, C.; Straumann, R., and Bucher, R.: Deutsche Ztschr. f. Chir. **236**:485, 1932.

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